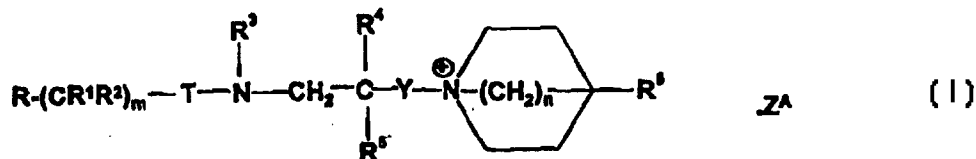




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(21) International Application Number: PCT/EP97/04414 (22) International Filing Date: 11 August 1997 (11.08.97) (30) Priority Data: 9617730.8 23 August 1996 (23.08.96) GB (71) Applicant (for GB only): PFIZER LIMITED [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). (71) Applicant (for all designated States except GB US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): MONAGHAN, Sandra, Marina [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). ALKER, David [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). BURNS, Christopher, John [AU/AU]; The University of Sydney, School of Chemistry F11, NSW 2006 (AU). (74) Agents: RUDDOCK, Keith, Stephen et al.; Pfizer Limited, European Patents Dept., Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: QUATERNARY AMMONIUM COMPOUNDS AS TACHYKININ ANTAGONIST

**(57) Abstract**

The present invention provides compounds of formula (I) as tachykinin receptor antagonists.

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QUATERNARY AMMONIUM COMPOUNDS AS TACHYKININ ANTAGONIST

5 This invention relates to quaternary ammonium compounds. More particularly, this invention relates to C₃-C₇ cycloalkyl-substituted quaternary ammonium compounds and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives.

10 The present compounds are antagonists of tachykinins, including NKA (neurokinin A), NKB (neurokinin B) and Substance P, acting at the human neurokinin-1(NK₁), neurokinin-2 (NK₂) and neurokinin-3 (NK₃) receptors.

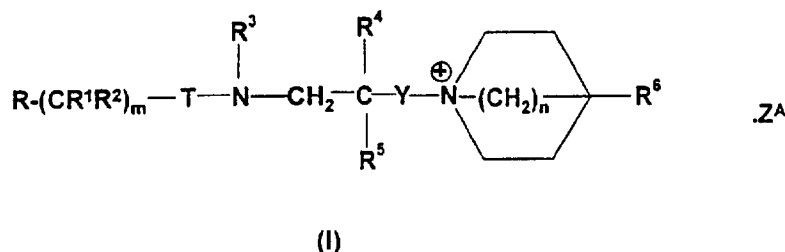
 These compounds are particularly useful as dual NK₁ and NK₂ receptor antagonists and can therefore be used for treating an inflammatory disease
15 such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, a disease caused by Helicobacter pylori or another urease-
20 positive Gram negative bacteria, a urogenital tract disorder such as incontinence, impotence, hyperreflexia or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis, atopic dermatitis, urticaria, eczematoid dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a proliferative disorder such as a
25 cancer or a disorder involving fibroblast proliferation, a vasospastic disease such as angiogenesis, angina or Reynaud's disease, a fibrosing or collagen disease such as atherosclerosis, scleroderma or eosinophilic fascioliasis, reflux sympathetic dystrophy such as shoulder/hand syndrome, an addiction disorder such as alcoholism, a stress-related somatic disorder, a peripheral neuropathy
30 such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn,

herpetic neuralgia or post-herpetic neuralgia, a neuropathological disorder such as Alzheimer's disease or multiple sclerosis, a disorder related to immune enhancement or suppression such as systemic lupus erythematosus, a
 5 rheumatic disease such as fibrositis, emesis, cough, acute or chronic pain, migraine, an ophthalmic disease such as proliferative retinopathy, influenza or a cold.

EP-A-0591040 discloses optionally phenyl- or benzyl-substituted quaternary ammonium compounds with tachykinin antagonist activity.

10 EP-A-0714891 discloses, *inter alia*, cyclohexylpiperidine and cyclohexylpiperazine derivatives as tachykinin receptor antagonists.

The present invention provides a compound of the formula:



15

wherein R is phenyl, C₃-C₇ cycloalkyl or heteroaryl, each of which being optionally benzo- or C₃-C₇ cycloalkyl-fused and optionally substituted, including in the benzo- or C₃-C₇ cycloalkyl-fused portion, by from 1 to 3 substituents each independently selected from C₁-C₄ alkyl, fluoro(C₁-C₄)alkyl, C₁-C₄ alkoxy, fluoro(C₁-C₄)alkoxy, C₂-C₄ alkanoyl, halo, C₁-C₄ alkoxycarbonyl, C₃-C₇
 20 cycloalkyl, -S(O)_p(C₁-C₄ alkyl), cyano, -NR⁷R⁸, -S(O)_pNR⁷R⁸, -NR⁷(C₁-C₄ alkanoyl) and -CONR⁷R⁸, or R is 2,3-dihydrobenzo[b]furanyl or chromanyl;

R^1 and R^2 are either each independently selected from H and C_1 - C_6 alkyl or, when taken together, represent C_2 - C_6 alkylene;

- 5 R^3 and R^4 are either each independently selected from H and C_1 - C_6 alkyl or, when taken together, represent unbranched C_1 - C_4 alkylene;

R^5 is phenyl, naphthyl, benzyl, thienyl, benzo[b]thienyl or indolyl, each of which being optionally substituted by from 1 to 3 substituents each independently
10 selected from C_1 - C_4 alkyl, fluoro(C_1 - C_4)alkyl, C_1 - C_4 alkoxy, halo and cyano, or R^5 is 1,3-benzodioxolan-4 or 5-yl or 1,4-benzodioxan-5 or 6-yl;

R^6 is C_3 - C_7 cycloalkyl optionally substituted by from 1 to 3 substituents each independently selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halo, cyano, fluoro(C_1 -
15 C_4)alkyl and fluoro(C_1 - C_4)alkoxy;

R^7 and R^8 are either each independently selected from H and C_1 - C_4 alkyl or, when taken together, represent C_4 - C_6 alkylene;

20 T is carbonyl;

Y is unbranched C_2 - C_4 alkylene;

Z^A is a pharmaceutically acceptable anion;

25

m is 0 or 1;

n is 1 or 2;

30 p is 0, 1 or 2; and

"heteroaryl", used in the definition of R, means thienyl or a 5- or 6-membered ring heteroaryl group containing either from 1 to 4 nitrogen heteroatoms, or 1 or 2 nitrogen heteroatom(s) and 1 oxygen or sulphur heteroatom,
5 with the proviso that when m is 0 and R is optionally fused and optionally substituted heteroaryl, said heteroaryl is linked by a ring carbon atom to T.

In the above definitions, "halo" means fluoro, chloro, bromo or iodo and alkyl and alkoxy groups having three or more carbon atoms, alkanoyl groups
10 having four carbon atoms and alkylene groups having two or more carbon atoms (except where stated) may be unbranched- or branched-chain.

Preferably, R is phenyl, optionally benzo- or C₃-C₇ cycloalkyl-fused, and optionally substituted, including in the benzo- or C₃-C₇ cycloalkyl-fused portion,
15 by from 1 to 3 substituents each independently selected from C₁-C₄ alkyl, halo, fluoro(C₁-C₄)alkyl and C₁-C₄ alkoxy, or R is 2,3-dihydrobenzo[b]furanyl.

More preferably, R is phenyl, naphthyl or 1,2,3,4-tetrahydronaphthyl, each of which being optionally substituted by from 1 to 3 substituents each independently selected from methyl, fluoro, bromo, trifluoromethyl, methoxy and
20 ethoxy, or R is 2,3-dihydrobenzo[b]furanyl.

Examples of R include phenyl, 2,3-dimethylphenyl, 3,5-dimethylphenyl, 3,5-dibromophenyl, 4-fluoro-3-trifluoromethylphenyl, 3,5-bis(trifluoromethyl)phenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 3,5-dimethoxy-4-methylphenyl, 3,5-

dimethyl-4-methoxyphenyl, 3,4,5-trimethoxyphenyl, 3,4,5-triethoxyphenyl, naphth-1-yl, 1,2,3,4-tetrahydronaphth-5-yl and 2,3-dihydrobenzo[b]furan-7-yl.

- 5 Most preferably, R is 3,5-bis(trifluoromethyl)phenyl or 3,5-dimethylphenyl.

Preferably, R¹ and R² are H.

- 10 Preferably, either R³ is C₁-C₄ alkyl and R⁴ is H, or R³ and R⁴, when taken together, represent C₂-C₃ alkylene.

More preferably, either R³ is methyl and R⁴ is H, or R³ and R⁴, when taken together, represent 1,2-ethylene or 1,3-propylene.

Most preferably, either R³ is methyl and R⁴ is H, or R³ and R⁴, when taken together, represent 1,2-ethylene.

15

Preferably, R⁵ is phenyl optionally substituted by 1, 2 or 3 halo substituents.

More preferably, R⁵ is phenyl optionally substituted by 1, 2 or 3 chloro substituents.

Most preferably, R⁵ is 3,4-dichlorophenyl.

20

Preferably, R⁶ is cyclohexyl optionally substituted as previously defined for the definition of R⁶ for a compound of the formula (I).

Most preferably, R⁶ is cyclohexyl.

- 25 Preferably, Y is 1,2-ethylene.

Z^A is a pharmaceutically acceptable anion such as chloride, bromide, nitrate, methanesulphonate, para-toluenesulphonate, benzenesulphonate, hydrogen sulphate or sulphate.

- 30 Preferably, Z^A is chloride or methanesulphonate.

Preferably, m is 0.

Preferably, n is 2.

5

Preferred examples of the compounds of the formula (I) are:

- (i) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-phenylacetyl]piperidin-3-yl)ethyl)quinuclidinium methanesulphonate;
- 10 (ii) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,4,5-trimethoxybenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium methanesulphonate;
- (iii) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methylphenylacetamido]butyl)quinuclidinium chloride;
- 15 (iv) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-3,5-dimethylbenzamido]butyl)quinuclidinium methanesulphonate;
- (v) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-3,5-bis(trifluoromethyl)phenylacetamido]butyl)quinuclidinium chloride;
- (vi) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-3,5-bis(trifluoromethyl)benzamido]butyl)quinuclidinium methanesulphonate;
- 20 (vii) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,5-dimethylbenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride;
- (viii) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methylnaphthalene-1-carboxamido]butyl)quinuclidinium methanesulphonate;
- 25 (ix) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-3,5-dimethylphenylacetamido]butyl)quinuclidinium methanesulphonate;
- (x) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-4-fluoro-3-trifluoromethylbenzamido]butyl)quinuclidinium methanesulphonate;

- (xi) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,5-bis(trifluoromethyl)phenylacetyl)piperidin-3-yl]ethyl)quinuclidinium methanesulphonate;
- 5 (xii) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,5-bis(trifluoromethyl)benzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride;
- (xiii) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,5-dimethylphenylacetyl)pyrrolidin-3-yl]ethyl)quinuclidinium methanesulphonate;
- 10 (xiv) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,4-dimethoxybenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride;
- (xv) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,5-dimethoxy-4-methylbenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride;
- (xvi) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(2,3-dihydrobenzo[b]furan-7-carbonyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride;
- 15 (xvii) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(2,3-dimethylbenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride;
- (xviii) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methylnaphthalene-1-acetamido]butyl)quinuclidinium methanesulphonate;
- 20 (xix) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-3,5-dibromobenzamido]butyl)quinuclidinium methanesulphonate;
- (xx) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-1,2,3,4-tetrahydronaphthalene-5-carboxamido]butyl)quinuclidinium methanesulphonate;
- 25 (xxi) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-3,5-bis(trifluoromethyl)benzamido]butyl)-1-azoniabicyclo[2.2.1]heptane methanesulphonate;
- (xxii) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,5-dimethoxybenzoyl)-pyrrolidin-3-yl]ethyl)quinuclidinium chloride;

- (xxiii) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,4,5-triethoxybenzoyl)-pyrrolidin-3-yl]ethyl)quinuclidinium chloride;
- (xxiv) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(4-fluoro-3-trifluoromethylbenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride;
- 5 (xxv) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,5-dimethyl-4-methoxybenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride; and
- (xxvi) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-3,5-bis-(trifluoromethyl)benzamido]butyl)quinuclidinium chloride;
- 10 and the alternative pharmaceutically acceptable salts thereof (re Z^A), and the individual (R)- and (S)- stereoisomers of any thereof.

A compound of the formula (I) contains one or more asymmetric carbon atoms and therefore exists in two or more stereoisomeric forms. The present invention includes the individual stereoisomers of the compounds of the formula (I) and mixtures thereof.

15

Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid.

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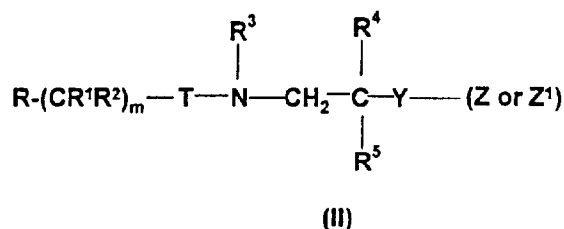
Examples of preferred individual stereoisomers include:

- (i) 4-cyclohexyl-1-(2-[3(S)-(3,4-dichlorophenyl)-1-phenylacetyl]piperidin-3-yl]ethyl)quinuclidinium methanesulphonate;
- 30 (ii) 4-cyclohexyl-1-(2-[3(S)-(3,4-dichlorophenyl)-1-(3,5-bis[trifluoromethyl]-phenylacetyl]piperidin-3-yl]ethyl)quinuclidinium methanesulphonate;

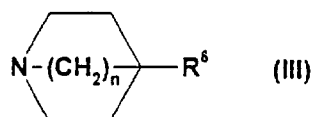
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- (iii) 4-cyclohexyl-1-(3(S)-[3,4-dichlorophenyl]-4-[N-methyl-3,5-bis-(trifluoromethyl)phenylacetamido]butyl)quinuclidinium chloride;
- (iv) 4-cyclohexyl-1-(3(S)-[3,4-dichlorophenyl]-4-[N-methyl-3,5-bis-(trifluoromethyl)benzamido]butyl)quinuclidinium methanesulphonate;
- (v) 4-cyclohexyl-1-(3(S)-[3,4-dichlorophenyl]-4-[N-methyl-4-fluoro-3-trifluoromethylbenzamido]butyl)quinuclidinium methanesulphonate;
- (vi) 4-cyclohexyl-1-(3(S)-[3,4-dichlorophenyl]-4-(N-methyl-3,5-bis(trifluoromethyl)benzamido]butyl)-1-azoniabicyclo[2.2.1]heptane methanesulphonate;
- (vii) 4-cyclohexyl-1-(3(S)-[3,4-dichlorophenyl]-4-[N-methyl-3,5-bis-(trifluoromethyl)benzamido]butyl)quinuclidinium chloride:
- and the alternative pharmaceutically acceptable salts thereof (re Z^A).

All the compounds of the formula (I) can be prepared by reaction of a compound of the formula:



wherein R, R^1 , R^2 , R^3 , R^4 , R^5 , T, Y and m are as previously defined for a compound of the formula (I), Z is a suitable leaving group capable of forming a pharmaceutically acceptable anion (Z^A) and Z^1 is a suitable leaving group, with a compound of the formula:



wherein R^6 and n are as previously defined for a compound of the formula (I), said process being followed by either (a), where Z^1 is a suitable leaving group, exchange for a pharmaceutically acceptable anion (Z^A), or (b), optionally, where
5 Z^A is a pharmaceutically acceptable anion, exchange for another pharmaceutically acceptable anion.

Preferred examples of Z are C_1 - C_4 alkanesulphonyloxy, benzenesulphonyloxy, para-toluenesulphonyloxy, chloro, bromo and iodo.

An example of Z^1 is trifluoromethanesulphonyloxy.

10 Preferably, the leaving group in the compound of the formula (II) forms a pharmaceutically acceptable anion (Z/Z^A), e.g. methanesulphonyloxy/methanesulphonate, and therefore anion exchange at the end of the process is unnecessary.

15 It is possible to exchange pharmaceutically acceptable anions (re Z^A) in the work-up procedure, e.g. methanesulphonate may be exchanged for chloride by treatment of the isolated compound or the crude reaction mixture with dilute aqueous hydrochloric acid solution.

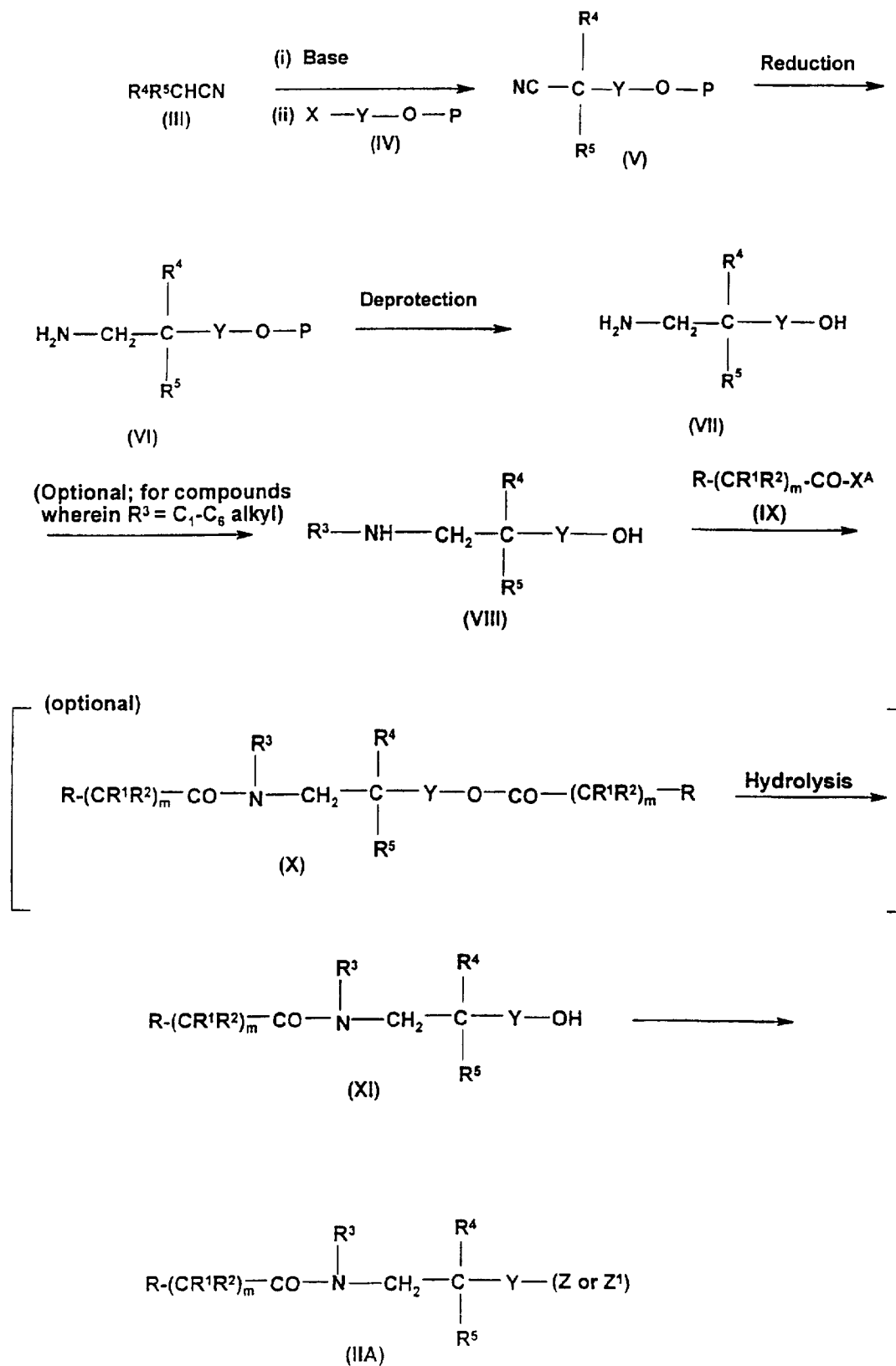
The reaction of the compounds (II) and (III) is generally carried out in a
20 suitable solvent, e.g. acetonitrile, at elevated temperatures, preferably at the reflux temperature thereof.

The starting materials of the formula (II) may be prepared by the following methods.

25 a) The starting materials of the formula (II) wherein R^3 and R^4 are each independently selected from H and C_1 - C_6 alkyl and R , R^1 , R^2 , R^5 , T , Y , Z , Z^1 and m are as previously defined for a compound of the formula (II) can be prepared as shown in Scheme 1:

11

SCHEME 1



wherein R, R¹, R², R³, R⁴, R⁵, Y, Z, Z¹ and m are as previously defined for this Scheme 1, P is a suitable protecting group and X and X^A are suitable leaving groups.

5 Examples of suitable protecting groups (P) can be found in the publication "Protective Groups in Organic Synthesis", T.W. Greene and P.G.M. Wuts, Second Edition, Wiley-Interscience.. A preferred example of P is tetrahydropyranyl.

 Examples of suitable leaving groups for X include chloro, bromo, iodo,
10 methanesulphonyloxy, trifluoromethanesulphonyloxy, benzenesulphonyloxy and para-toluenesulphonyloxy.

 Examples of suitable leaving groups for X^A are chloro and bromo.

 In a typical procedure, a nitrile of the formula (III) is treated with a suitable base, e.g. sodium hydride, in a suitable solvent, e.g. tetrahydrofuran,
15 and is then alkylated with a compound of the formula (IV). The nitrile of the formula (V) prepared is reduced to an amine of the formula (VI) using conventional conditions, e.g. catalytic hydrogenation. Deprotection of the amine of the formula (VI) can be achieved using the conditions described in the above Greene publication. Where a compound of the formula (II) where R³ is
20 C₂-C₆ alkyl is desired, the amine of the formula (VII) is subjected to reductive amination using an aldehyde of the formula (C₁-C₅ alkyl)CHO, a suitable reducing agent, e.g. BH₃.S(CH₃)₂, and a suitable solvent, e.g. tetrahydrofuran. Where a compound of the formula (II) where R³ is methyl is desired, the amine of the formula (VII) is first treated with formic anhydride and the product
25 is then reduced using a suitable reducing agent, e.g. BH₃.S(CH₃)₂. A compound of the formula (VIII) (which, where R³ is H, corresponds to a compound of the formula (VII)) may then be acylated with at least two mole equivalents of a compound of the formula (IX), preferably in the presence of a suitable acid acceptor, e.g. triethylamine, and using a suitable solvent, e.g.
30 dichloromethane. Hydrolysis of a compound of the formula (X) under suitable

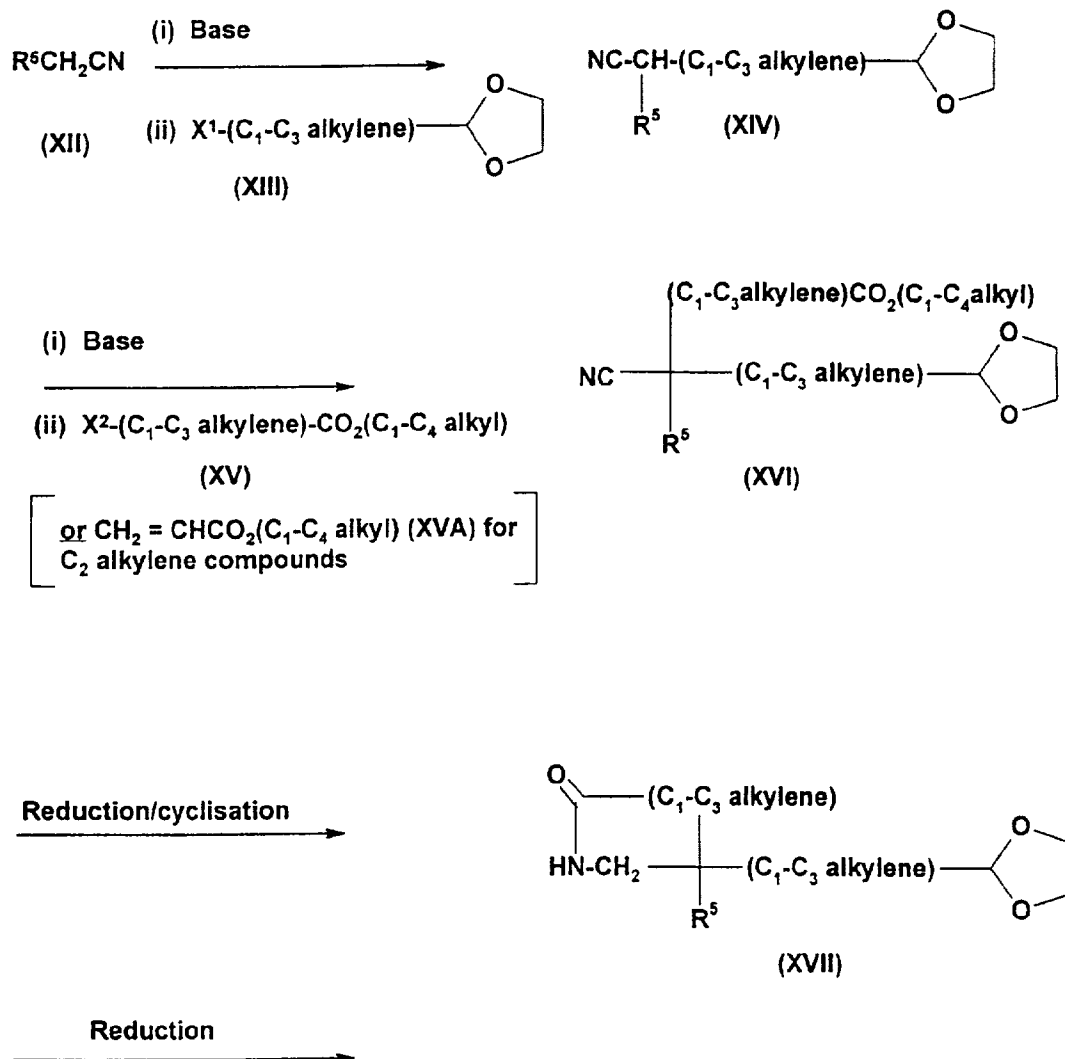
conditions, e.g. aqueous sodium hydroxide in methanol, provides an alcohol of the formula (XI). Alternatively, a compound of the formula (VIII) can be converted directly to a compound of the formula (XI) using approximately one mole equivalent of a compound of the formula (IX) under the above acylation conditions. A compound of the formula (XI) can be converted to a compound of the formula (IIA) using conventional conditions. For example, an alcohol of the formula (XI) can be converted to a compound of the formula (IIA) where Z is methanesulphonyloxy by treatment with methanesulphonyl chloride, triethylamine and dichloromethane, and a compound of the formula (IIA) wherein Z¹ is trifluoromethanesulphonyloxy may be prepared by treating an alcohol of the formula (XI) with trifluoromethanesulphonic anhydride, optionally in the presence of a suitable acid acceptor, and in a suitable solvent, e.g. dichloromethane.

15

b) The starting materials of the formula (II) where R³ and R⁴, taken together, represent unbranched C₁-C₄ alkylene and R, R¹, R², R⁵, T, Y, Z, Z¹ and m are as previously defined for a compound of the formula (II) can be prepared as shown in Scheme 2.

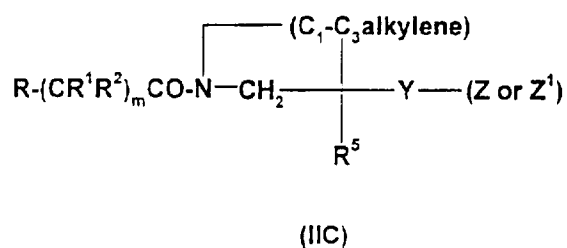
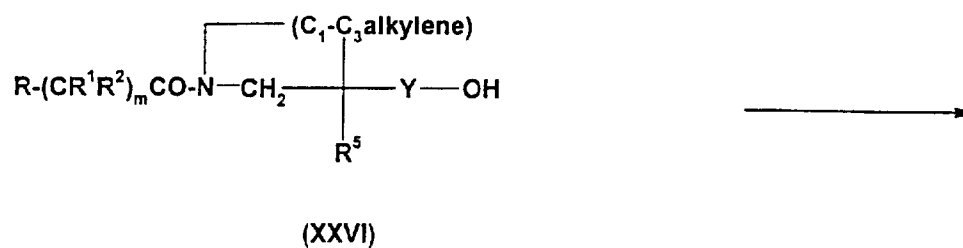
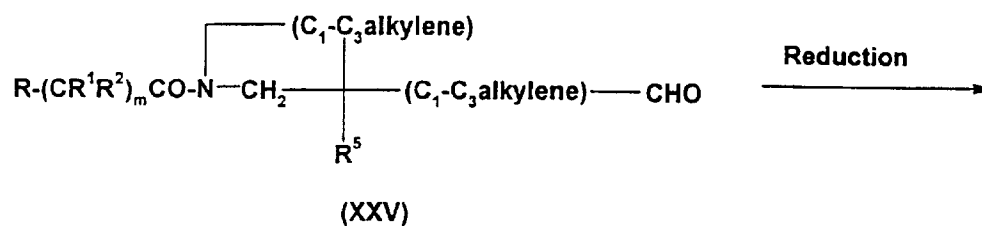
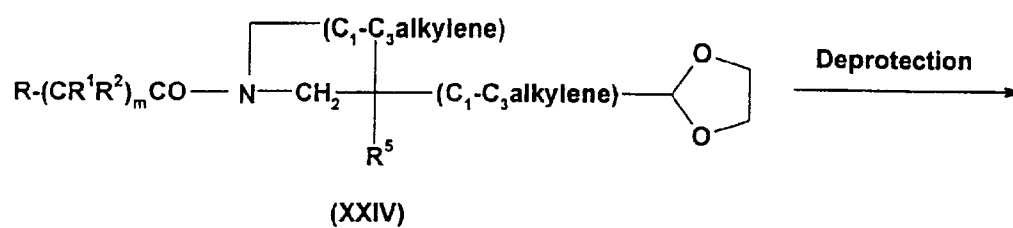
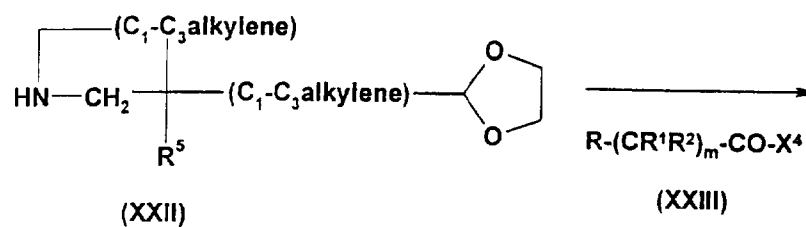
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SCHEME 2



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SCHEME 2 Contd./



wherein R, R¹, R², R⁵, Y, Z, Z¹ and m are as previously defined for this Scheme 2, X¹ and X² are each suitable leaving groups such as one of those previously defined for X and X⁴ is a suitable leaving group such as chloro or bromo.

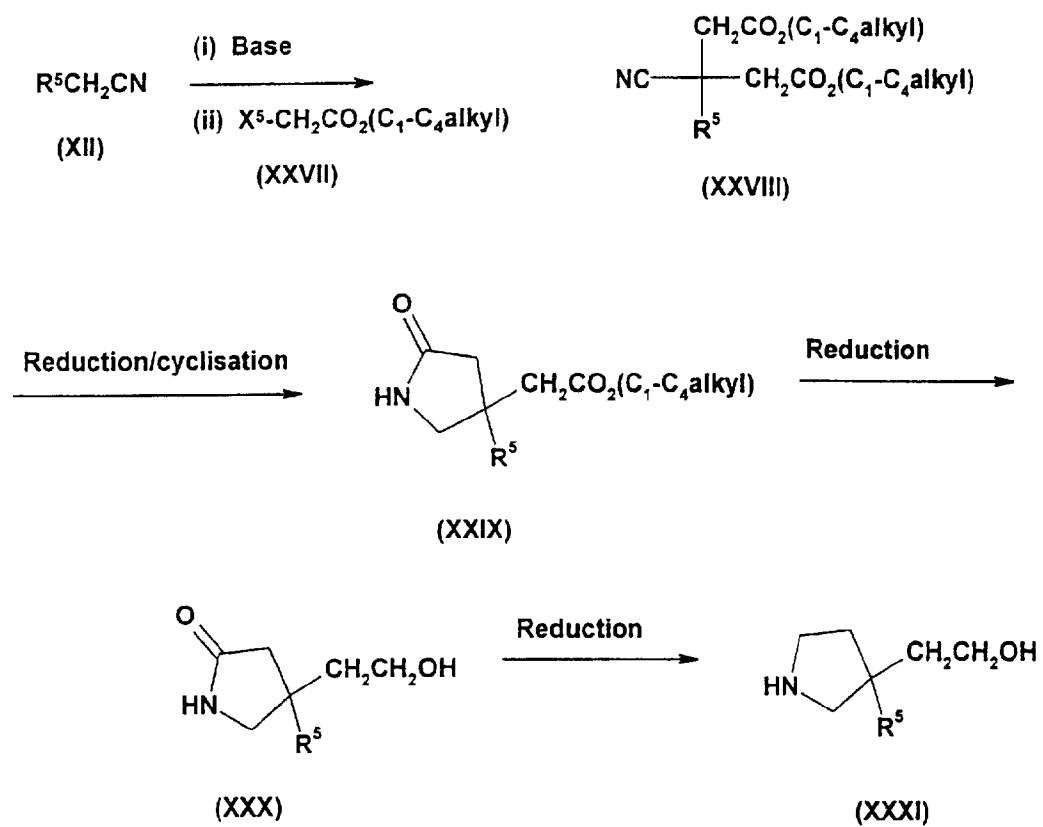
- 5 In a typical procedure, a nitrile of the formula (XII) is treated with a suitable base, e.g. sodium hydride or lithium hexamethyldisilazide, in a suitable solvent, e.g. tetrahydrofuran, and then alkylated with a compound of the formula (XIII). The nitrile of the formula (XIV) prepared is either further alkylated with a compound of the formula (XV) under similar conditions used for
- 10 the previous step, or is treated with an acrylate of the formula (XVA) in the presence of a suitable base, e.g. sodium methoxide, and in a suitable solvent, e.g. methanol. Reductive cyclisation of a compound of the formula (XVI) is achieved under a hydrogen atmosphere using a suitable catalyst, e.g. platinum (II) oxide, in the presence of a suitable solvent, e.g. acetic acid. It is also
- 15 possible to convert a compound of the formula (XVI) to a compound of the formula (XVII) by hydrolysis of a compound of the formula (XVI) using, e.g., aqueous sodium hydroxide solution, followed by reductive cyclisation of the corresponding carboxylic acid produced under the conditions described above for a compound of the formula (XVI). A lactam of the formula (XVII) is then
- 20 reduced to a cyclic amine of the formula (XXII) under standard conditions, e.g. lithium aluminium hydride/tetrahydrofuran. Acylation of a compound of the formula (XXII) with a compound of the formula (XXIII), optionally in the presence of a suitable acid acceptor, e.g. triethylamine, and in a suitable solvent, e.g. dichloromethane, provides a compound of the formula (XXIV).
- 25 Acylation can also be achieved by conventional condensation of a compound of the formula (XXII) with an appropriate carboxylic acid. This compound can be deprotected under conventional conditions such as those described in the above Greene publication, e.g. using aqueous hydrochloric acid solution/tetrahydrofuran. The aldehyde of the formula (XXV) prepared can be
- 30 reduced to an alcohol of the formula (XXVI) under standard conditions, e.g.

sodium borohydride/ethanol. This alcohol can be transformed to a compound of the formula (IIC) using similar conditions to those previously described for the conversion of a compound of the formula (XI) to a compound of the formula (IIA).

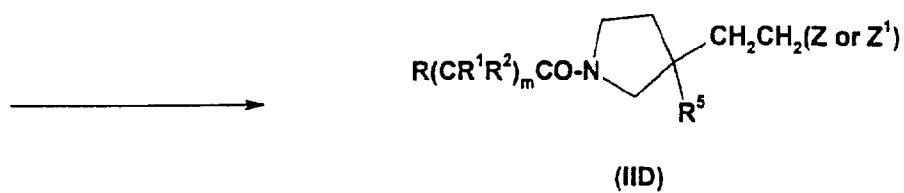
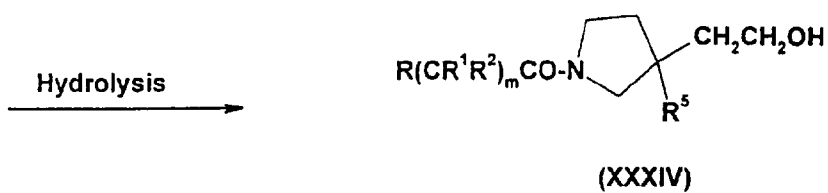
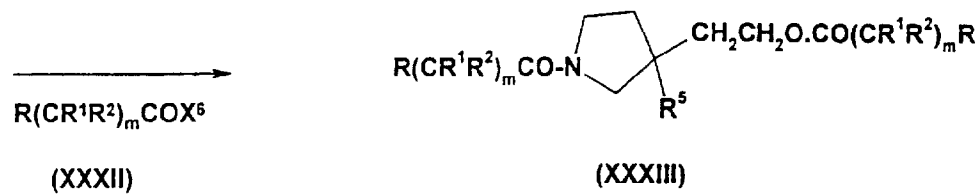
c) The starting materials of the formula (II) wherein Y is ethylene, R^3 and R^4 , taken together, represent ethylene and R, R^1 , R^2 , R^5 , T, Y, Z, Z^1 and m are as previously defined for a compound of the formula (II) can be prepared as shown in Scheme 3.

18

SCHEME 3



SCHEME 3 Contd./



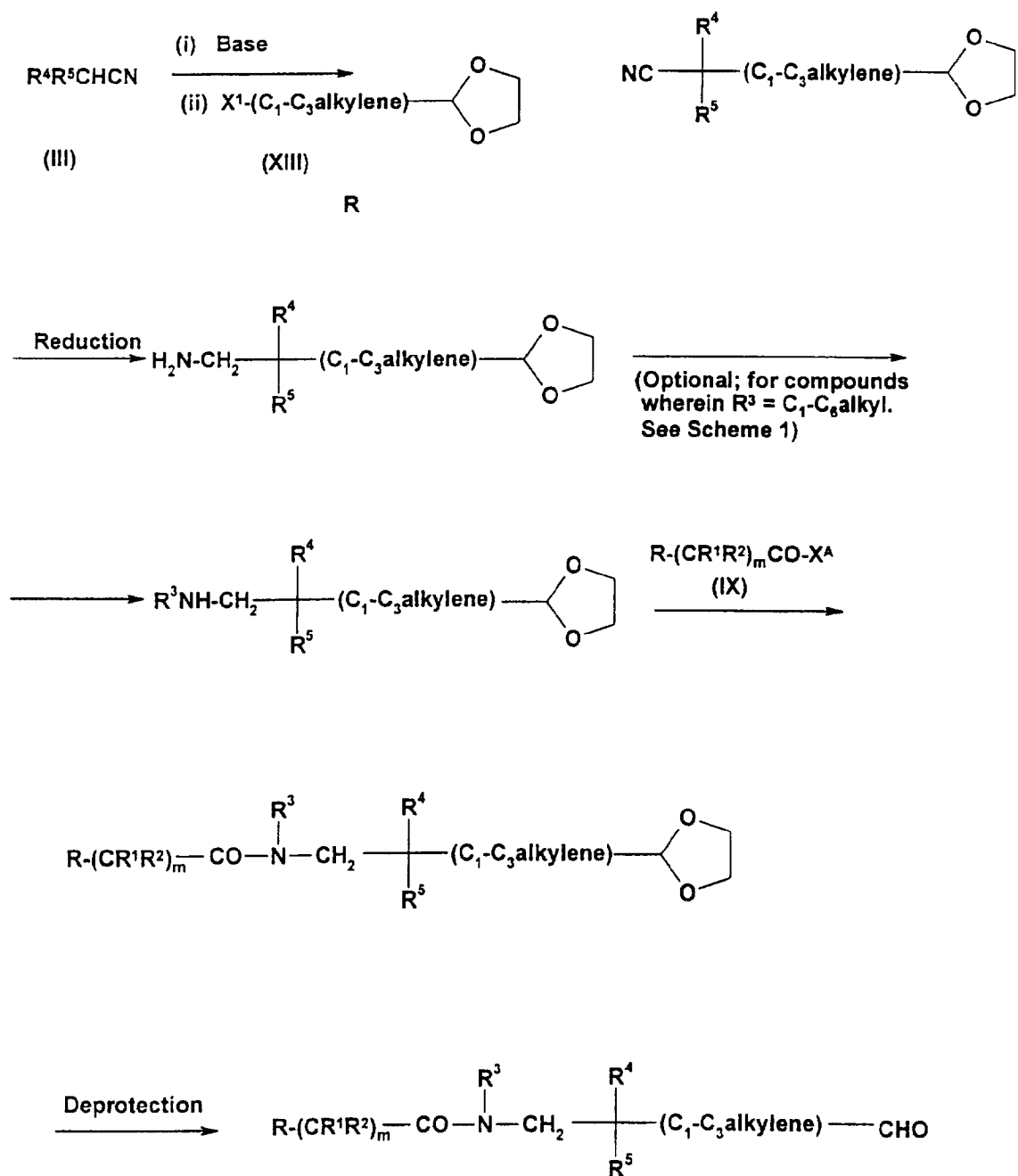
wherein R, R¹, R², R⁵, Z, Z¹ and m are as previously defined for this Scheme 3, X⁵ is a suitable leaving group such as one of those previously defined for X and X⁶ is a suitable leaving group such as chloro or bromo.

- 5 In a typical procedure, a nitrile of the formula (XII) is alkylated with a compound of the formula (XXVII) using a suitable base, e.g. sodium hexamethyldisilazide, and in a suitable solvent, e.g. tetrahydrofuran. Reduction of a compound of the formula (XXVIII) using a suitable reducing agent, e.g. sodium borohydride/cobalt (II) chloride, and in a suitable solvent, e.g. ethanol, followed by in situ intramolecular cyclisation of the intermediate amine provides a lactam of the formula (XXIX). Reduction of the ester group of this lactam using a suitable reducing agent, e.g. lithium aluminium hydride, and in a suitable solvent, e.g. tetrahydrofuran, provides an alcohol of the formula (XXX) that can be reduced to a pyrrolidine of the formula (XXXI) using a suitable reducing agent, e.g. diborane, and in a suitable solvent, e.g. tetrahydrofuran. Acylation of this pyrrolidine (optionally as an acid addition salt, e.g. hydrochloride) with a compound of the formula (XXXII), preferably in the presence of a suitable acid acceptor, e.g. triethylamine, and in a suitable solvent, e.g. dichloromethane, provides a compound of the formula (XXXIII) that can be hydrolysed to a compound of the formula (XXXIV) using conventional conditions, e.g. aqueous sodium hydroxide in methanol or ethanol. A compound of the formula (XXXIV) can be converted to a compound of the formula (IID) using conventional conditions such as those previously described for the conversion of a compound of the formula (XI) to a compound of the formula (IIA).
- 10
15
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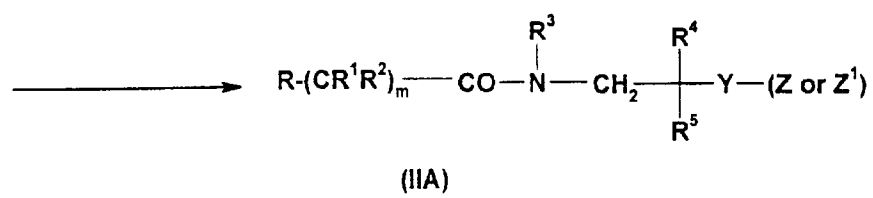
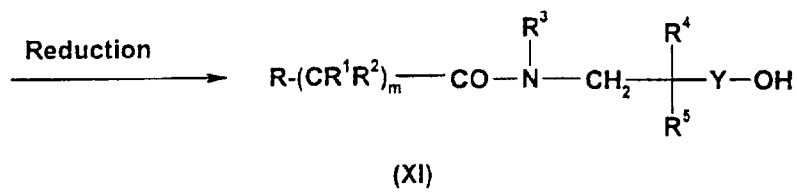
- d) The starting materials of the formula (II) wherein R³ and R⁴ are each independently selected from H and C₁-C₆ alkyl and R, R¹, R², R⁵, T, Y, Z, Z¹ and m are as previously defined for a compound of the formula (II) can be prepared as shown in Scheme 4.
- 30

21

SCHEME 4



22

SCHEME 4 Contd./

23

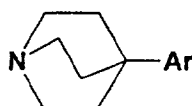
wherein R, R¹, R², R³, R⁴, R⁵, Y, Z, Z¹ and m are as previously defined for this Scheme 4 and X¹ and X^A are as previously defined in methods (a) and (b).

The reactions may be carried out by similar procedures to those
5 described for the analogous transformations described in the preceding methods (a) -(c).

The starting materials of the formula (III) may be prepared by the following methods.

10 i) The compounds of the formula (III) wherein n is 2 can be prepared by a similar method to that described in Chem.Ber., 108, 3475 (1975).

Alternatively, the compounds of the formula (III) wherein n is 2 and R⁶ is cyclohexyl optionally substituted as previously defined for the definition of R⁶ for a compound of the formula (I) can be prepared by catalytic hydrogenation of a
15 compound of the formula:



(XXXV)

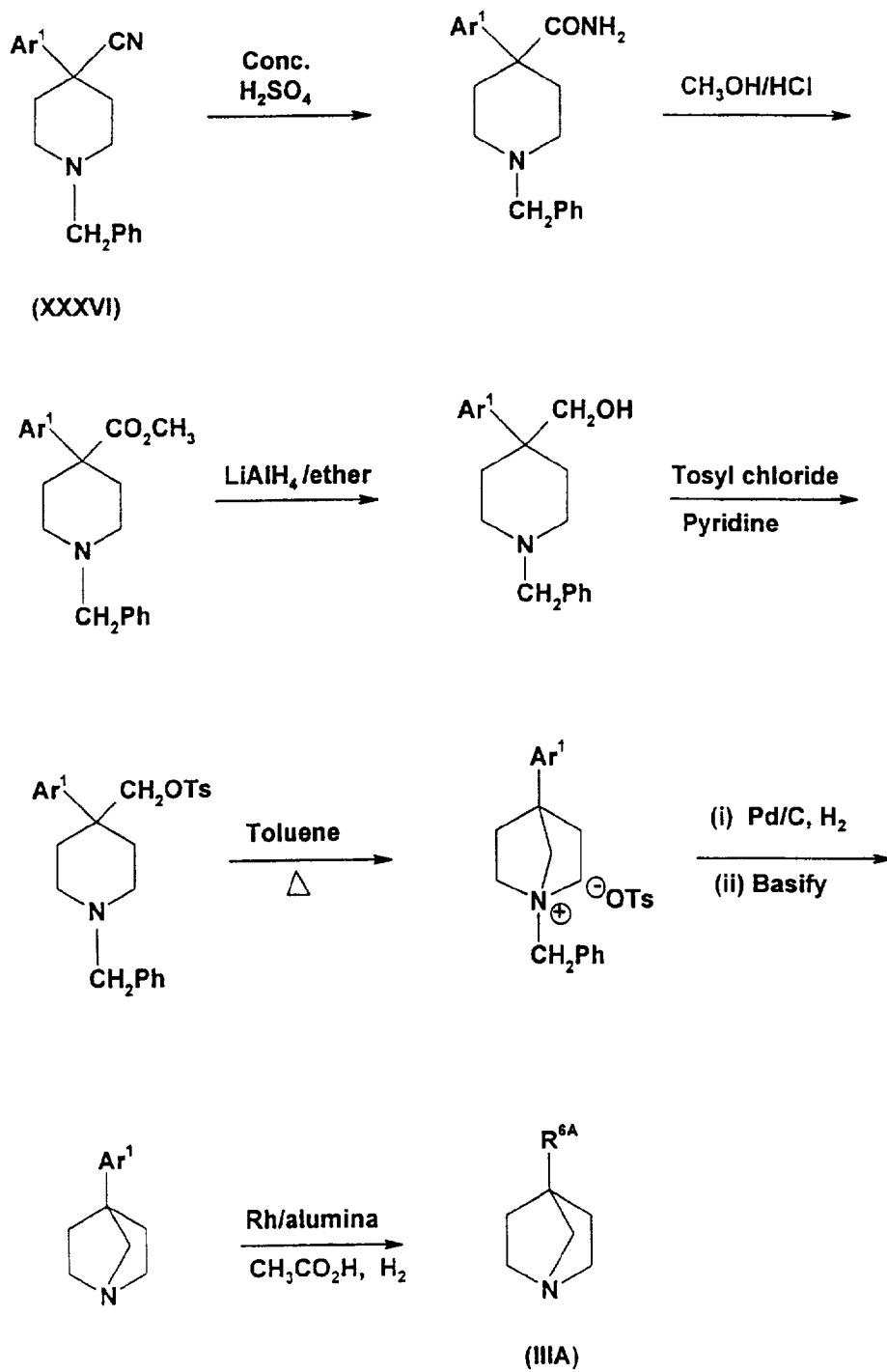
wherein Ar is phenyl optionally substituted as previously defined for the above
20 definition of R⁶. The reduction can be carried out under a hydrogen atmosphere using a suitable catalyst, e.g. rhodium-on-alumina, and in a suitable solvent, e.g. acetic acid. The compounds of the formula (XXXV) may be prepared by similar methods to those described in Chem. Ber., 108, 3475 (1975) and J. Org. Chem., 22, 1484 (1957).

25

ii) The compounds of the formula (III) wherein n is 1 and R⁶ is cyclohexyl optionally substituted as previously defined for the definition of R⁶ for a compound of the formula (I) can be prepared conventionally as shown in Scheme 5.

24

SCHEME 5



wherein Ar¹ is phenyl optionally substituted as previously defined for the above definition of R⁶ for Scheme 5, R^{6A} is cyclohexyl optionally substituted as previously defined for the above definition of R⁶ for Scheme 5, "Ph" is phenyl and "Ts" is para-toluenesulphonyloxy. The starting materials of the formula (XXXVI) may be prepared by conventional procedures.

All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well known to those skilled in the art with reference to literature precedents and the Examples and Preparations hereto.

The affinity of the compounds of the formula (I) for the human NK₁ receptor can be determined in vitro by determining their ability to inhibit [³H]-Substance P binding to membranes prepared from the human IM9 cell line expressing the human NK₁ receptor using a modification of the method described in McLean, S.*et al*, J.Pharm.Exp.Ther., 267, 472-9 (1993) in which whole cells were used.

The affinity of the compounds of formula (I) for the human NK₂ receptor can be determined in vitro by determining their ability to compete with [³H]-NKA (neurokinin A) for binding to membranes prepared from Chinese hamster ovary cells expressing the cloned human NK₂ receptor. In this method, washed Chinese hamster ovary cell membranes are prepared as described for the previous method where IM9 cells are used instead. The membranes are incubated (90 min, 25°C) with [³H]-NKA and with a range of concentrations of the test compound. Non-specific binding is determined in the presence of 10µM NKA.

The NK₁ receptor antagonist activity of the compounds of the formula (I) can be determined in vitro by testing their ability to antagonise the contractile effects of Substance P in de-epithelialised guinea pig tracheal strips. Tissues

can be prepared from guinea pigs (350-600g) which are killed by stunning and exsanguination. The excised trachea is cleared of connective tissue and opened longitudinally, opposite the trachealis muscle band. The epithelial layer
5 can then be removed by rubbing the inner surface of the trachea with a cotton bud. Strips of approximately 4 cartilage bands wide are cut and mounted under 1g tension in organ baths containing Krebs solution (composition: NaCl 118mM, KCl 4.6mM, NaHCO₃ 25mM, KH₂PO₄ 1.4mM, MgSO₄ 1.2mM, CaCl₂ 2.5mM, glucose 11mM) at 37°C and gassed with 95% O₂/5% CO₂. The potential action
10 of Substance P on the NK₂ receptor population found in this tissue can be prevented by the inclusion of the selective NK₂ receptor antagonist \pm SR-48,968 (1 μ M) in the Krebs buffer solution. Additionally, indomethacin (3 μ M) is added to remove the influence of endogenous prostanoids. Tension changes of the tissue in response to cumulative addition of the agonist Substance P are
15 recorded isometrically. The potency of the compounds of the formula (I) can be assessed by the magnitude of shift induced in the Substance P dose response curve, using standard Schild analysis, following 30 minutes incubation of the compound with the tissue.

The de-epithelialised guinea pig trachea strip preparation may also be
20 used to evaluate the NK₂ receptor antagonist activity of the compounds of the formula (I) in vitro by using the selective NK₂ receptor agonist [β -Ala⁸]NKA₍₄₋₁₀₎ as the contractile agent. For such studies, strips are prepared and mounted in organ baths as described above, using Krebs solution of the following composition: NaCl 118mM, KCl 4.6mM, NaHCO₃ 25mM, KH₂PO₄ 1.4mM,
25 MgSO₄ 1.2mM, CaCl₂ 2.5mM, glucose 11mM, indomethacin 3 μ M. The potency of the compounds may be assessed by the magnitude of the shift induced in the [β -Ala⁸]NKA₍₄₋₁₀₎ dose response curve, using standard Schild analysis, following 30 minutes incubation of the compound with the tissue.

The compounds of the formula (I) can be tested for NK₃ receptor antagonist activity, *in vitro*, by testing their ability to antagonise the contractile
5 effects of the selective NK₃ receptor agonist senktide in the guinea-pig ileum using the method of Maggi *et al*, Br.J.Pharmacol., 101, 996-1000 (1990).

For human use, the compounds of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard
10 pharmaceutical practice.

For example, they can be administered orally or sublingually in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents.

15 They can be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

20 For oral and parenteral administration to human patients, the daily dosage level of the compounds of the formula (I) will be from 0.01 to 20mg/kg (in single or divided doses) and preferably will be from 0.1 to 5mg/kg.

Thus tablets or capsules of the compounds will contain from 1mg to 0.5g of active compound for administration singly or two or more at a time, as
25 appropriate. The physician in any event will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this
30 invention.

The compounds of formula (I) can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container or a nebuliser with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the formula (I) and a suitable powder base such as lactose or starch.

Aerosol formulations are preferably arranged so that each metered dose or "puff" of aerosol contains from 20 μ g to 1000 μ g of a compound of formula (I) for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 20 μ g to 20mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

Alternatively, the compounds of the formula (I) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. For example, they can be incorporated into a cream consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin, or they can be incorporated, at a concentration of from 1 to 10% by weight, into an ointment consisting of a white wax or white soft paraffin base together with such stabilisers and preservatives as may be required. The compounds of the formula (I) may also be transdermally administered by the use of a skin patch.

It is to be appreciated that reference to treatment includes prophylaxis as well as the alleviation of established symptoms of the disease.

Thus the invention further provides:-

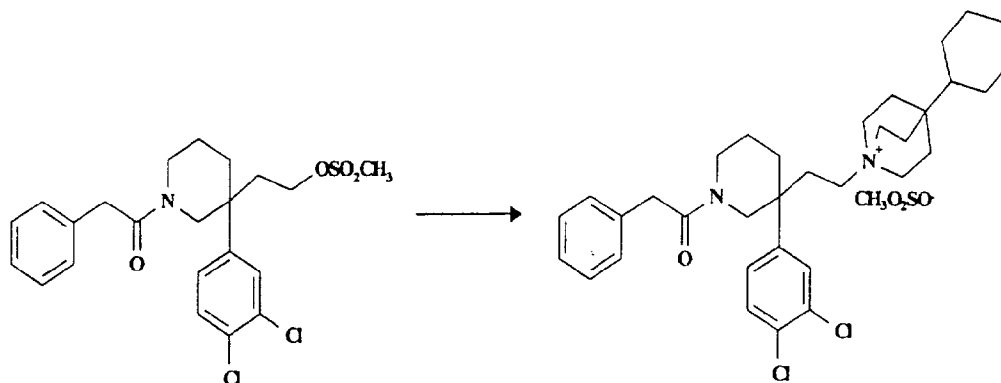
- 5 (i) a pharmaceutical composition comprising a compound of the formula (I) together with a pharmaceutically acceptable diluent or carrier;
- (ii) a compound of the formula (I) or a pharmaceutically acceptable composition thereof, for use as a medicament;
- (iii) the use of a compound of the formula (I), or of a pharmaceutically
10 acceptable composition thereof, for the manufacture of a medicament for the treatment of a disease by producing an antagonist effect on a tachykinin receptor or on a combination of tachykinin receptors;
- (iv) use as in (iii) where the antagonist effect is on the human NK₁ and NK₂ tachykinin receptors;
- 15 (v) use as in (iii) or (iv) where the disease is an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal
20 incontinence, colitis or Crohn's disease, a disease caused by Helicobacter pylori or another urease-positive Gram negative bacteria, a urogenital tract disorder such as incontinence, hyperreflexia or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis, atopic dermatitis or rhinitis, a
25 hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, emesis, cough, migraine or acute or chronic pain;

- (vi) a method of treatment of a human to treat a disease by producing an antagonist effect on a tachykinin receptor or on a combination of tachykinin receptors, which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable composition thereof;
- (vii) a method as in (vi) where the antagonist effect is on the human NK₁ and NK₂ tachykinin receptors; and
- (viii) a method as in (vi) or (vii) where the disease is an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, a disease caused by Helicobacter pylori or another urease-positive Gram negative bacteria, a urogenital tract disorder such as incontinence, hyperreflexia or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis, atopic dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, emesis, cough, migraine or acute or chronic pain.

The following Examples illustrate the preparation of the compounds of the formula (I):-

EXAMPLE 1

4-Cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-phenylacetyl]piperidin-3-yl)ethyl)quinuclidinium methanesulphonate



5

The compound of Preparation 8 (0.47g) and 4-cyclohexylquinuclidine (0.2g) (see Preparation 20) were dissolved in acetonitrile (10ml) and heated under reflux for 8 hours. The solvent was removed under reduced pressure and the resulting residue dissolved in dichloromethane and the solvent removed under reduced pressure. The crude product was chromatographed on silica eluting with a solvent gradient of 95:5 changing to 93:7, by volume, dichloromethane : methanol to give the title compound (0.64g) as a white foam.

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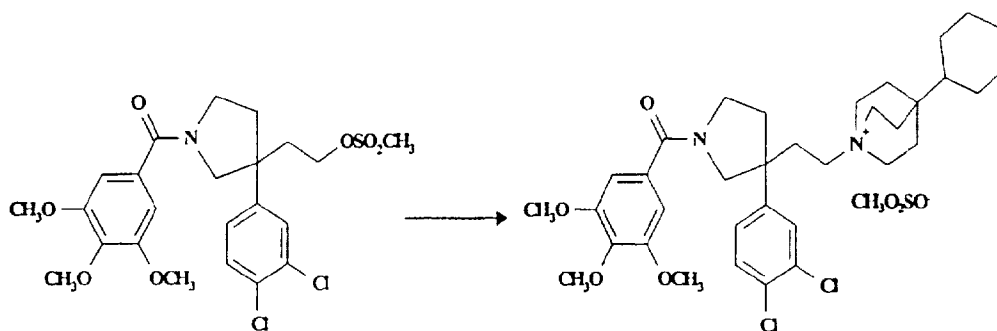
$^1\text{H-NMR}$ (CDCl_3): δ = 7.16-7.48 (8H, m), 4.31 (1H, d), 3.69-3.91 (3H, m), 3.26-3.42 (7H, m), 3.02-3.22 (2H, m), 2.80-2.90 (2H, m), 2.00-2.30 (4H, m), 1.50-1.90 (15H, m), 1.03-1.23 (4H, m), 0.80-0.95 (2H, m) ppm.

15

Found: C, 64.44; H, 7.69; N, 4.62. $\text{C}_{35}\text{H}_{48}\text{Cl}_2\text{N}_2\text{O}_4\text{S}$. 0.2 mol water requires C, 64.64; H, 7.35; N, 4.31%.

EXAMPLE 24-Cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,4,5-trimethoxybenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium methanesulphonate

5



The compound of Preparation 13 (0.7g) and 4-cyclohexylquinuclidine (0.3g) (see Preparation 20) were dissolved in acetonitrile (10ml) and heated under reflux for 18 hours. The solvent was removed under reduced pressure and the resulting residue dissolved in dichloromethane and the solvent removed under reduced pressure. The crude product was chromatographed on silica eluting with a solvent gradient of 98:2 changing to 90:10, by volume, dichloromethane : methanol to give a white foam which was dissolved in dichloromethane and filtered. The solvent was removed under reduced pressure and the product trituated with diethyl ether to give the title compound (0.55g) as a white solid.

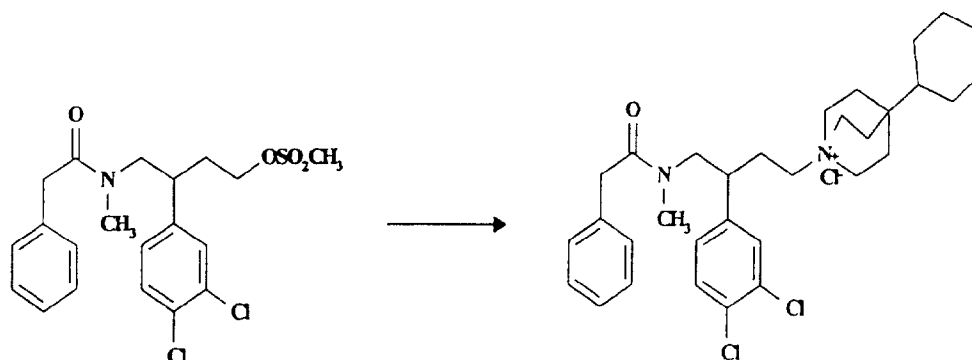
$^1\text{H-NMR}$ (CDCl_3): δ = 7.20-7.50 (3H, m), 6.74-6.82 (2H, m), 3.80-4.10 (11H, m), 3.30-3.57 (9H, m), 2.75 (3H, s), 2.58 (2H, m), 2.22 (2H, m), 1.60-1.85 (12H, m), 1.05-1.25 (4H, m), 0.87 (2H, m) ppm.

Found: C, 59.06; H, 7.29; N, 3.82. $\text{C}_{36}\text{H}_{50}\text{Cl}_2\text{N}_2\text{O}_7\text{S}$ requires C, 59.58; H, 6.95; N, 3.86%.

33

EXAMPLE 3

4-Cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methylphenylacetamido]
butyl)quinuclidinium chloride



5

The compound of Preparation 16 (0.4g) and 4-cyclohexylquinuclidine (0.26g) (see Preparation 20) were dissolved in acetonitrile (10ml) and heated under reflux for 20 hours. The solvent was removed under reduced pressure and the resulting residue dissolved in dichloromethane (50ml) and washed with 2N aqueous hydrochloric acid solution (3x 25ml). The organic phase was separated and the solvent removed under reduced pressure. The crude product was chromatographed on silica eluting with a solvent gradient of 95:5 changing to 90:10, by volume, dichloromethane : methanol to give the title compound (0.21g) as a white foam.

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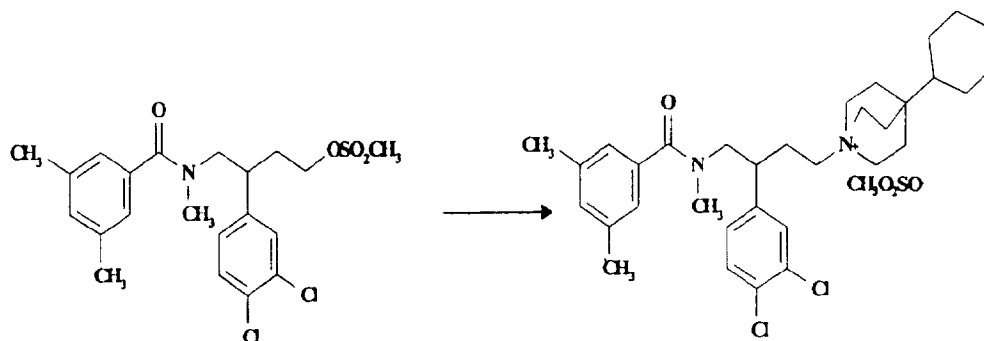
¹H-NMR (CDCl₃): δ = 7.11-7.40 (8H, m), 3.85-4.01 (2H, m), 3.30-3.75 (9H, m), 3.19 (1H, m), 2.98 (3H, s), 2.90 (1H, m), 1.40-2.20 (13H, m), 1.05-1.26 (4H, m), 0.80-0.95 (2H, m) ppm.

20

34

EXAMPLE 4

4-Cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-3,5-dimethylbenzamido]-butyl)quinuclidinium methanesulphonate



5

The title compound was prepared in an analogous fashion to the compound of Example 3 using the compound of Preparation 17 and 4-cyclohexylquinuclidine (see Preparation 20) as the starting materials, but without treatment with

10 hydrochloric acid in the work-up procedure.

¹H-NMR (CDCl₃): δ = 7.25-7.50 (3H, m), 6.99 (1H, s), 6.81 (2H, s), 3.85-4.02 (2H, m), 3.35-3.69 (8H, m), 2.81 (6H, s), 2.29-2.35 (7H, s), 2.10 (1H, m), 1.60-1.90 (12H, m), 1.05-1.25 (4H, m), 0.80-0.95 (2H, m) ppm.

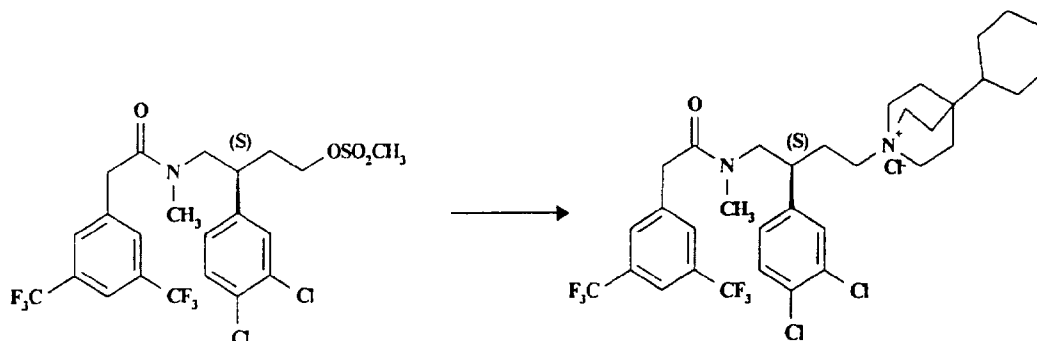
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Found: C, 60.90; H, 7.39; N, 4.15. C₃₄H₄₈Cl₂N₂O₄S. 0.5 mol water. 0.17 mol dichloromethane requires C, 60.80; H, 7.36; N, 4.15%.

35

EXAMPLE 5

4-Cyclohexyl-1-(3(S)-[3,4-dichlorophenyl]-4-[N-methyl-3,5-bis(trifluoromethyl)phenylacetamido]butyl)quinuclidinium chloride



5

The compound of Preparation 19 (2.5g) and 4-cyclohexylquinuclidine (1.0g) (see Preparation 20) were dissolved in acetonitrile (20ml) and heated under reflux for 18 hours. The solvent was removed under reduced pressure and the resulting residue dissolved in dichloromethane (50ml) and washed with 2N aqueous hydrochloric acid solution (3x 25ml) and then brine. The organic phase was collected and the solvent removed under reduced pressure. The crude product was chromatographed on silica eluting with a solvent gradient of 95:5 changing to 93:7, by volume, dichloromethane:methanol to give the title compound (0.64g) as a white foam.

15

$^1\text{H-NMR}$ (CDCl_3): δ = 7.75 (3H, s), 7.41 (1H, d), 7.31 (1H, s), 7.16 (1H, dd), 4.00-4.15 (3H, m), 3.80 (1H, d), 3.60-3.70 (3H, m), 3.36-3.50 (3H, m), 3.21 (1H, m), 3.16 (3H, s), 2.85 (1H, m), 2.39 (1H, m), 2.02 (1H, m), 1.60-1.90 (12H, m), 1.05-1.27 (4H, m), 0.82-0.98 (2H, m) ppm.

20

Found: C, 56.39; H, 5.96; N, 3.74. $\text{C}_{34}\text{H}_{41}\text{Cl}_3\text{F}_6\text{N}_2\text{OS}$. 0.5 mol water requires C, 56.47; H, 5.72; N, 3.87%.

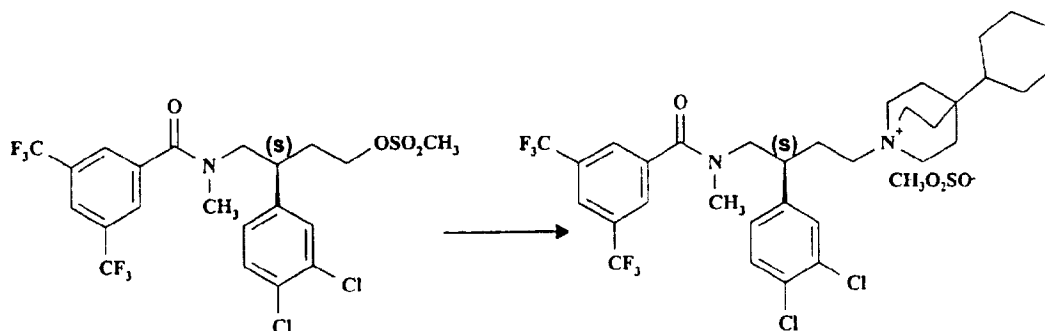
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$[\alpha]_{\text{D}}^{25}$ -50.2° (c = 1 mg/ml in ethanol).

36

EXAMPLE 6

4-Cyclohexyl-1-(3(S)-[3,4-dichlorophenyl]-4-[N-methyl-3,5-
bis(trifluoromethyl)benzamido]butyl)quinuclidinium methanesulphonate



The compound of Preparation 22 (0.58g) and 4-cyclohexylquinuclidine (0.24g)
 10 (see Preparation 20) were dissolved in acetonitrile (8ml) and heated under
 reflux for 18 hours. The solvent was removed under reduced pressure and the
 resulting residue dissolved in dichloromethane before removal of the solvent
 under reduced pressure. The crude product was chromatographed on silica gel
 eluting with a solvent gradient of 95:5 changing to 85:5, by volume,
 15 methanol:dichloromethane to give the title compound (0.65g) as a white foam.

$^1\text{H-NMR}$ (CDCl_3): δ = 7.89 (1H,s), 7.80 (2H,s), 7.46 (2H,m), 7.30 (1H,m), 4.11
 (2H,m), 3.30-3.65 (8H,m), 2.95 (3H,s), 2.78 (3H,s), 2.70 (1H,m), 2.47 (1H,m),
 2.00 (1H,m), 1.60-1.90 (11H,m), 1.05-1.25 (4H,m), 0.80-0.95 (2H,m) ppm.

20

Found: C, 53.10; H, 5.64; N, 3.33. $\text{C}_{34}\text{H}_{42}\text{Cl}_2\text{F}_6\text{N}_2\text{O}_4\text{S}$. 0.1 mol
 dichloromethane requires C, 53.32; H, 5.54; N, 3.64%.

25

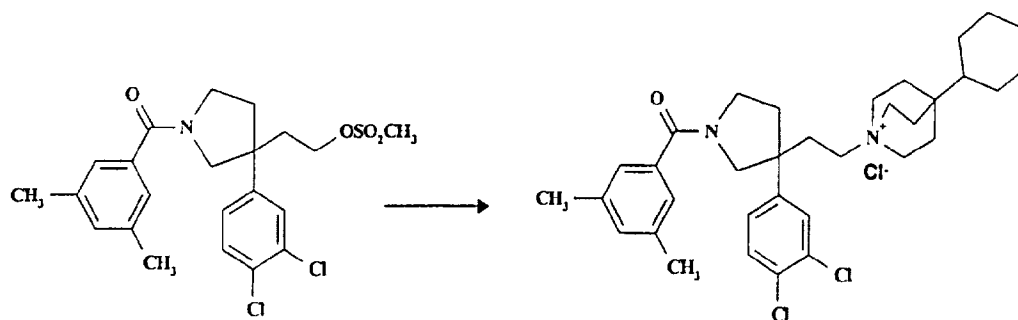
$[\alpha]_{\text{D}}^{25}$ - 20.0° (c = 1mg/ml in methanol).

37

EXAMPLE 7

4-Cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,5-dimethylbenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride

5



The title compound was prepared in an analogous fashion to the compound of Example 3 using the compound of Preparation 24 and 4-cyclohexylquinuclidine (see Preparation 20) as the starting materials.

10

$^1\text{H-NMR}$ (CDCl_3): δ = 7.20-7.50 (3H,m), 7.0-7.10 (3H,m), 3.40-4.05 (10H,m), 2.50-2.90 (2H,m), 2.15-2.40 (8H,m), 1.50-1.90 (13H,m), 1.00-1.25 (4H,m), 0.70-0.90 (2H,m) ppm.

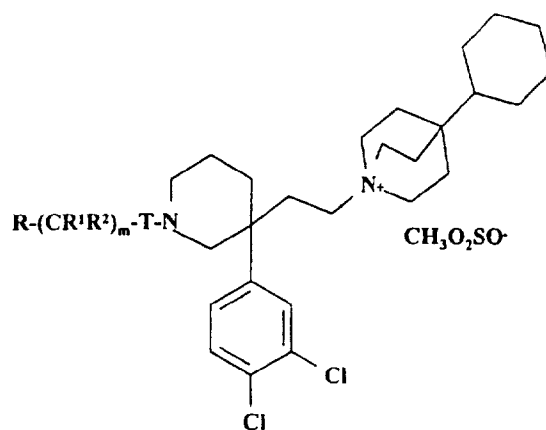
15

Found: C, 63.91; H, 7.64; N, 4.39. $\text{C}_{34}\text{H}_{45}\text{Cl}_3\text{N}_2\text{O}$. 0.33 mol dichloromethane. 0.66 mol water requires C, 63.99; H, 7.35; N, 4.35%.

38

EXAMPLES 8 and 9

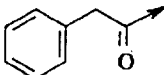
The compounds of the following tabulated Examples (Table 1) of the general
5 formula:



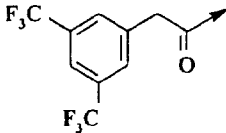
were prepared by a similar method to that of Example 1 using the appropriate
mesylate and 4-cyclohexylquinuclidine (see Preparation 20) starting materials

10

TABLE 1

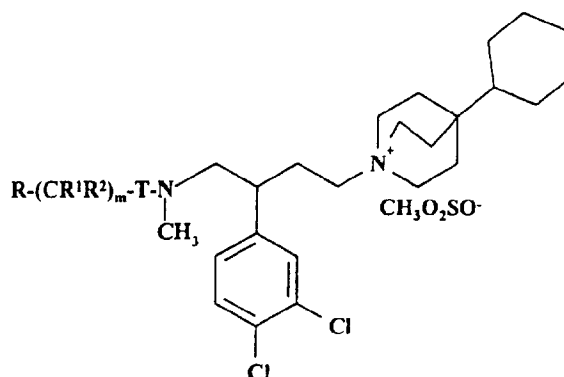
Ex. no.	Mesylate starting material Prep. no.	Stereo-chemistry	R-(CR ¹ R ²) _m -T-	Analytical Data
8	40	S		¹ H-NMR (CDCl ₃): δ = 7.16-7.48 (8H,m), 4.31 (1H,d), 3.69-3.91 (3H,m), 3.26-3.42 (7H,m), 3.02-3.22 (2H,m), 2.80-2.90 (2H,m), 2.00-2.30 (4H,m), 1.50-1.90 (15H,m), 1.03-1.23 (4H,m), 0.80-0.95 (2H,m) ppm. Found: C, 62.78; H, 7.46; N, 4.25. C ₃₅ H ₄₈ Cl ₂ N ₂ O ₄ S. 1.0 mol water requires C, 63.14; H, 7.57; N, 4.21%.

-40-

9	41	S		<p>¹H-NMR (CDCl₃): δ = 7.82 (2H,s), 7.75 (1H,s), 7.46 (1H, m), 7.32 (1H,s), 7.18 (1H,m), 4.66 (1H,d), 4.41 (1H,d), 4.02 (1H,d), 3.85 (1H,d), 2.50-3.50 (12H,m), 2.30 (1H,m), 2.06 (1H,m), 1.60-1.83 (16H,m), 1.05-1.25 (4H,m), 0.80-0.92 (2H,m) ppm.</p> <p>Found: C, 54.47; H, 5.86; N, 3.48.</p> <p>C₃₇H₄₆Cl₂F₆N₂O₄S. 0.7 mol water requires C, 54.71; H, 5.88; N, 3.45%.</p>
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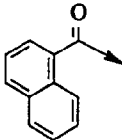
EXAMPLES 10-16

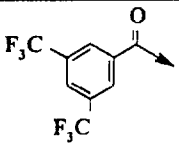
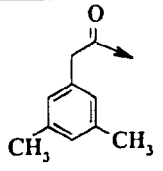
The compounds of the following tabulated Examples (Table 2) of the general
5 formula:

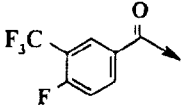
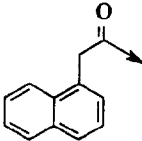
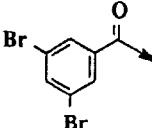


were prepared by a similar method to that of Example 6 using the appropriate mesylate and 4-cyclohexylquinuclidine (see Preparation 20) starting materials.

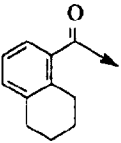
TABLE 2

Ex. no.	Mesylate starting material Prep. no.	Stereo-chemistry	R-(CR ¹ R ²) _m -T-	Analytical Data
10	50	R/S		<p>¹H-NMR (CDCl₃): δ = 7.82 (2H,d), 7.63 (1H,s), 7.35-7.52 (7H,m), 3.80-4.30 (2H,m), 3.20-3.60 (8H,m), 2.77 (3H,s), 2.69 (3H,s), 2.40 (1H,m), 2.15 (1H, m), 1.48-1.81 (12H,m), 0.85-1.20 (4H,m), 0.70-0.82 (2H,m) ppm.</p> <p>Found: C, 61.13; H, 6.73; N, 4.02. C₃₆H₄₆Cl₂N₂O₄S. 0.5 mol dichloromethane requires C, 61.21; H, 6.61; N, 3.91%.</p>

11	51	R/S		<p>¹H-NMR (CDCl₃): δ = 7.89 (1H,s), 7.80 (2H,s), 7.46 (2H,m), 7.30 (1H,m), 4.11 (2H,m), 3.30-3.65 (8H,m), 2.95 (3H,s), 2.78 (3H,s), 2.70 (1H,m), 2.47 (1H,m), 2.00 (1H,m), 1.60-1.90 (11H,m), 1.05-1.25 (4H,m), 0.80-0.95 (2H,m) ppm.</p> <p>Found: C, 53.56; H, 5.55; N, 3.64. C₃₄H₄₂Cl₂F₆N₂O₄S requires C, 53.76; H, 5.57; N, 3.69%.</p>
12	52	R/S		<p>¹H-NMR (CDCl₃): δ = 7.30-7.40 (2H,m), 7.19 (1H,dd), 6.88 (1H,s), 6.82 (2H,s), 4.01 (1H,), 3.81 (1H,m), 3.61 (2H,d), 3.20-3.52 (9H,m), 2.97 (3H,s), 2.80 (3H,s), 2.29 (6H,s), 2.14 (1H, m), 1.60-1.95 (12H,m), 1.05-1.25 (4H,m), 0.80-0.95 (2H,m) ppm.</p> <p>Found: C, 61.87; H, 7.68; N, 4.20. C₃₅H₅₀Cl₂N₂O₄S. 0.16 mol dichloromethane requires C, 62.13; H, 7.46; N, 4.12%.</p>

13	53	S		<p>¹H-NMR (CDCl₃): δ = 7.75 (1H,m), 7.63 (1H,d), 7.44 (2H, m), 7.20-7.30 (2H,m), 4.10-4.27 (2H,m), 3.30-3.65 (8H,m), 3.00 (3H,s), 2.80 (2.2H,s), 2.70 (0.8H,m), 2.41 (1H,m), 2.00 (1H,m), 1.60-1.85 (12H,m), 1.05-1.30 (4H,m), 0.80-0.95 (2H,m) ppm.</p> <p>Found: C, 54.89; H, 6.12; N, 3.91. C₃₃H₄₂Cl₂F₄N₂O₄S. 0.5 mol water requires C, 55.15; H, 6.03; N, 3.90%.</p>
14	54	R/S		<p>¹H-NMR (CDCl₃): δ= 7.97 (1H,d), 7.85 (1H,d), 7.75 (1H, d), 7.30-7.60 (5H,m), 7.15-7.25 (2H,m), 3.95-4.20 (3H,m), 3.70-3.82 (1H,m), 3.08-3.42 (11H, m), 2.80 (3H,s), 2.70 (1H,m), 2.10 (1H,m), 1.55-1.90 (12H, m), 1.05-1.30 (4H,m), 0.80-0.92 (2H,m) ppm.</p> <p>Found: C, 62.44; H, 7.04; N, 3.90. C₃₇H₄₈Cl₂N₂O₄S. 0.5 mol water. 0.2 mol dichloromethane requires C, 62.60; H, 6.83; N, 3.92%.</p>
15	55	R/S		<p>¹H-NMR (CDCl₃): δ = 7.66 (1H,s), 7.25-7.50 (5H,m), 3.95-4.10 (2H,m), 3.30-3.70 (8H,m), 2.70-2.90 (6H,m), 2.38 (1H,m), 2.02 (1H,m), 1.60-1.90 (12H, m), 1.05-1.26 (4H,m), 0.80-0.95 (2H,m) ppm.</p>

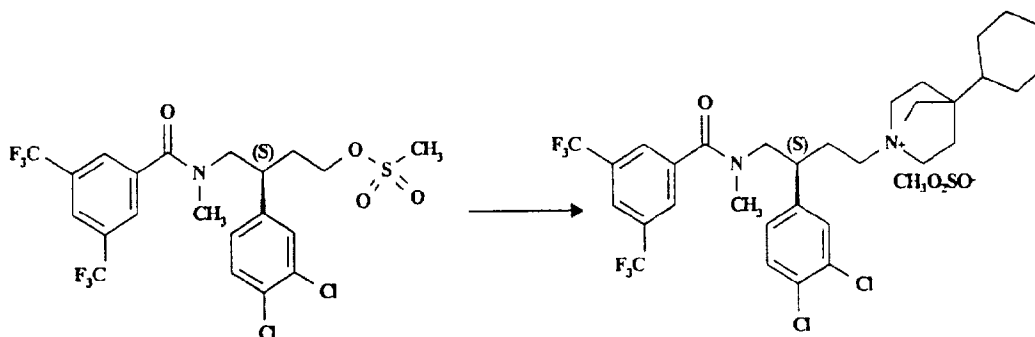
44

16	56	R/S		¹ H-NMR (CDCl ₃): δ = 7.20-7.50 (4H, m), 6.90-7.10 (2H, m), 4.02 (1H, m), 3.30-3.80 (9H, m), 2.62-2.90 (9H, m), 2.34 (1H, m), 2.03 (1H, m), 1.52-1.90 (17H, m), 1.05-1.30 (4H, m), 0.80-0.95 (2H, m) ppm. Found: C, 60.67; H, 7.24; N, 3.87. C ₃₆ H ₅₀ Cl ₂ N ₂ O ₄ S. 0.5 mol dichloromethane requires C, 60.87; H, 7.13; N, 3.89%.
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EXAMPLE 17

4-Cyclohexyl-1-(3(S)-[3,4-dichlorophenyl]-4-[N-methyl-3,5-bis(trifluoromethyl)-benzamido]butyl)-1-azoniabicyclo[2.2.1]heptane methanesulphonate



10

The title compound was prepared in an analogous fashion to that described in Example 6 using the compounds of Preparations 30 and 22 as starting materials.

15

45

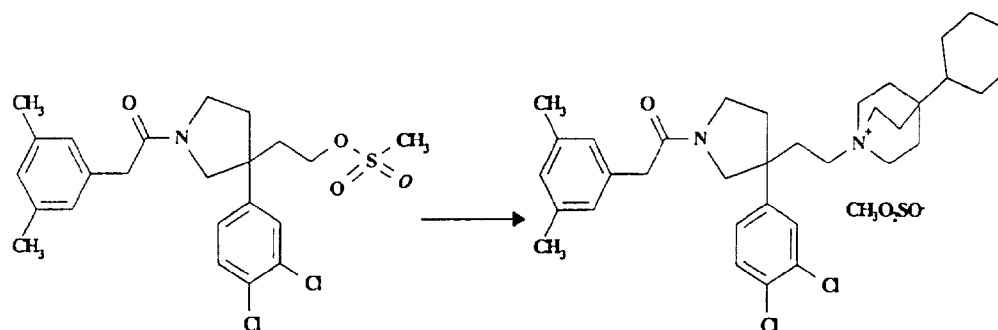
$^1\text{H-NMR}$ (CDCl_3): δ = 7.90 (1H, s), 7.80 (2H, s), 7.46 (2H, d), 7.30 (1H, m), 4.30 (1H, m), 4.11 (1H, m), 3.95 (1H, m), 3.25-3.70 (8H, m), 3.05 (1H, m), 2.95 (3H, s), 2.80 (3H, s), 2.50 (1H, m), 2.00-2.20 (3H, m), 1.50-1.90 (6H, m), 1.00-1.30 (6H, m) ppm.

Found: C, 52.45; H, 5.53; N, 3.69. $\text{C}_{33}\text{H}_{40}\text{Cl}_2\text{F}_6\text{N}_2\text{O}_4\text{S}$. 0.1 mol dichloromethane requires C, 52.72; H, 5.37; N, 3.71%.

10

EXAMPLE 18

4-Cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,5-dimethylphenyl)acetyl]-pyrrolidin-3-yl]ethyl)quinuclidinium methanesulphonate



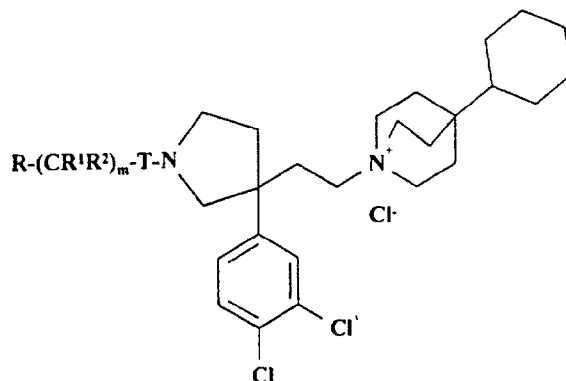
15 The title compound was prepared following a similar procedure to that described in Example 2 using the compound of Preparation 72 and 4-cyclohexylquinuclidine (see Preparation 20) as starting materials.

$^1\text{H-NMR}$ (CDCl_3): δ = 7.11-7.43 (4H, m), 6.84 (2H, s), 3.32-3.75 (13H, m), 2.78 (3H, m), 2.60-2.75 (1H, m), 2.26 (6H, s), 2.08 (2H, m), 1.58-1.80 (13H, m), 1.15 (4H, m), 0.88 (2H, m) ppm.

Found: C, 63.56; H, 7.86; N, 4.06. $\text{C}_{36}\text{H}_{50}\text{Cl}_2\text{N}_2\text{O}_3\text{S}$ requires C, 63.80; H, 7.44; N, 4.13%.

EXAMPLES 19-27

The compounds of the following Examples (Table 3) of the general formula:

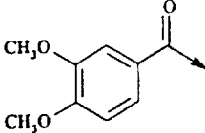
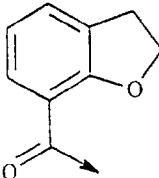


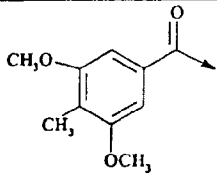
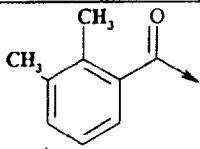
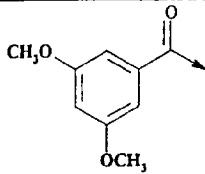
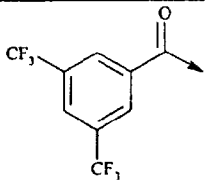
5

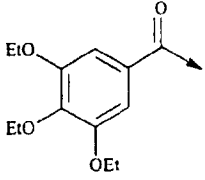
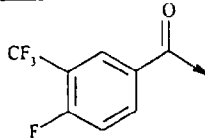
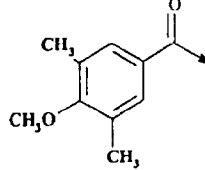
were prepared by a similar method to that of Example 3 using 4-cyclohexylquinuclidine (see Preparation 20) and the appropriate mesylates as starting materials.

10

TABLE 3

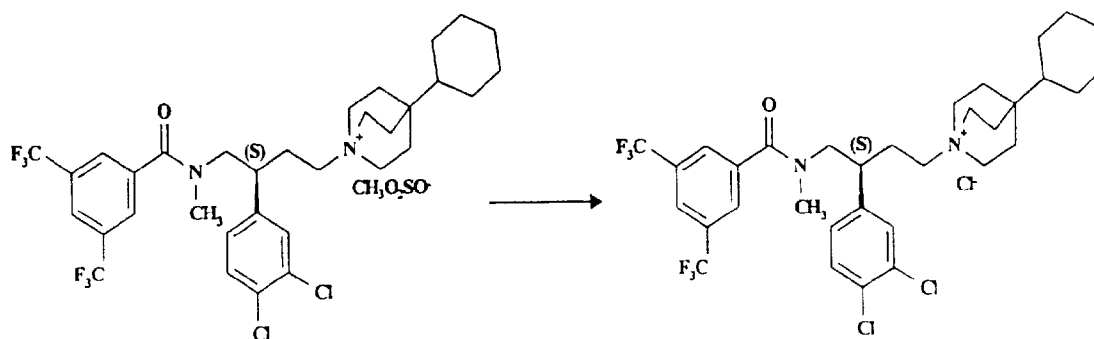
Ex. no.	Mesylate starting material	$R-(CR^1R^2)_m-T-$	Analytical Data
19	73		^1H-NMR ($CDCl_3$): δ = 7.48 (1H,d), 7.22 (4H, m), 6.90 (1H,m), 3.90 (10H,m), 3.56 (8H,m), 2.16-2.76 (4H,m), 1.77 (7H,m), 1.62 (4H,m), 1.14 (4H,m), 0.87 (2H,m) ppm. Found: C, 61.45; H, 7.19; N, 4.24. $C_{34}H_{45}Cl_3N_2O_3$. 1.4 mol water requires, C, 61.74; H, 7.13; N, 4.24%.
20	74		^1H-NMR ($CDCl_3$): δ = 7.14-7.49 (5H,m), 6.88 (1H,d), 4.12 (2H,t), 3.44-3.85 (10H,m), 3.26 (2H,m), 2.72 (2H,m), 2.52 (1H,m), 2.00-2.28 (3H,m), 1.79 (8H,m), 1.65 (3H,m), 1.16 (4H, m), 0.88 (2H,m) ppm. Found: C, 63.38; H, 7.12; N, 4.42. $C_{34}H_{43}Cl_3N_2O_2$. 1.4 mol water requires, C, 63.48; H, 7.17; N, 4.35%.

21	75		<p>$^1\text{H-NMR}$ (CDCl_3): $\delta = 7.20\text{--}7.48$ (3H,m), 6.70 (2H,d), 4.02 (1H,m), 3.85 (7H,m), 3.45-3.62 (7H,m), 2.81 (1H,m), 2.06-2.62 (6H,m), 1.86 (3H,s), 1.74 (8H,m), 1.60 (3H,m), 1.10 (4H,m), 0.84 (2H,m) ppm.</p> <p>Found: C, 62.13; H, 7.35; N, 4.23. $\text{C}_{35}\text{H}_{47}\text{Cl}_3\text{N}_2\text{O}_3$. 0.23 mol dichloromethane. 0.67 mol water requires C, 62.07; H, 7.22; N, 4.11%.</p>
22	76		<p>$^1\text{H-NMR}$ (CDCl_3): $\delta = 6.96\text{--}7.48$ (6H,m), 3.68-4.08 (3H,m), 3.40-3.61 (6H,m), 3.11 (1H,m), 2.88 (1H,m), 2.60 (2H,m), 2.28 (4H,m), 2.14 (3H,s), 1.58-1.88 (13H,m), 1.12 (4H,m), 0.85 (2H,m) ppm.</p> <p>Found: C, 64.30; H, 7.63; N, 4.40. $\text{C}_{34}\text{H}_{45}\text{Cl}_3\text{N}_2\text{O}$, 0.07 mol dichloromethane. 1.5 mol water requires C, 64.25; H, 7.62; N, 4.40%.</p>
23	77		<p>$^1\text{H-NMR}$ (CDCl_3): $\delta = 7.18\text{--}7.50$ (3H,m), 6.64 (2H,s), 6.50 (1H,s), 3.74-4.10 (8H,m), 3.58 (10H,m), 2.49-2.76 (2H,m), 2.23 (2H,m), 1.62-1.85 (7H,m), 1.48 (4H,m), 1.20 (4H,m), 0.88 (2H,m) ppm.</p> <p>Found: C, 62.16; H, 7.15; N, 4.28. $\text{C}_{34}\text{H}_{45}\text{Cl}_3\text{N}_2\text{O}_3$. 1.4 mol water requires C, 61.75; H, 7.28; N, 4.24%.</p>
24	78		<p>$^1\text{H-NMR}$ (CDCl_3): $\delta = 7.94\text{--}8.06$ (3H,m), 7.23-7.50 (3H,m), 4.06 (2H,m), 3.83 (2H,m), 3.47-3.68 (6H,m), 2.28-2.82 (4H,m), 1.80 (10H,m), 1.65 (3H,m), 1.02-1.23 (4H,m), 0.80-0.95 (2H,m) ppm.</p> <p>Found: C, 56.39; H, 5.73; N, 3.86. $\text{C}_{34}\text{H}_{39}\text{Cl}_3\text{F}_6\text{N}_2\text{O}$. 0.67 mol water requires C, 56.40; H, 5.62; N, 3.87%.</p>

25	79	 <p>(Et = ethyl)</p>	¹ H-NMR (CDCl ₃): δ = 7.44 (1H,m), 7.26 (2H, m), 6.76 (2H,d), 3.88-4.12 (9H,m), 3.40-3.80 (9H,m), 2.84 (1H,m), 2.20-2.60 (3H,m), 1.75 (7H,m), 1.61 (2H,m), 1.40 (11H,m), 1.13 (4H, m), 0.86 (2H,m) ppm. Found: C, 62.54; H, 7.63; N, 3.61. C ₃₈ H ₅₃ Cl ₃ N ₂ O ₄ . 1.2 mol water requires C, 62.53; H, 7.65; N, 3.84%.
26	80		¹ H-NMR (CDCl ₃): δ = 7.90 (2H,m), 7.10-7.50 (4H,m), 3.24-4.12 (12H,m), 2.18-2.71 (4H,m), 1.80 (6H,m), 1.65 (2H,m), 1.52 (3H,m), 1.15 (4H,m), 0.86 (2H,m) ppm.
27	81		¹ H-NMR (CDCl ₃): δ = 7.16-7.48 (5H,m), 3.46-4.20 (15H,m), 2.50-2.78 (2H,m), 2.06-2.34 (8H, m), 1.78 (8H,m), 1.64 (3H,m), 1.15 (4H,m), 0.87 (2H,m) ppm. Found: C, 64.31; H, 7.69; N, 4.23. C ₃₅ H ₄₇ Cl ₃ N ₂ O ₂ . 1.0 mol water requires C, 64.46; H, 7.57; N, 4.29%.

EXAMPLE 28

- 5 4-Cyclohexyl-1-(3(S)-[3,4-dichlorophenyl]-4-[N-methyl-3,5-bis-(trifluoromethyl)benzamido]butyl)quinuclidinium chloride



4-Cyclohexyl-1-(3(S)-[3,4-dichlorophenyl]-4-[N-methyl-3,5-bis-(trifluoromethyl)benzamido]butyl)quinuclidinium methanesulphonate (1.5g) (see Example 6) was dissolved in dichloromethane (25ml) and washed three times
5 with 2N aqueous hydrochloric acid solution (25ml), followed by brine. The organic phase was dried over anhydrous sodium sulphate and the solvent removed under reduced pressure to give the title compound (1.04g) as a white foam.

10 $^1\text{H-NMR}$ (CDCl_3): δ = 7.89 (1H, s), 7.66 (2H, s), 7.30-7.50 (3H, m), 4.19-4.31 (1H, m), 3.40-4.00 (9H, m), 2.87 (3H, s), 2.32-2.49 (1H, m), 2.09-2.25 (1H, m), 1.60-1.90 (12H, m), 0.80-1.33 (6H, m) ppm

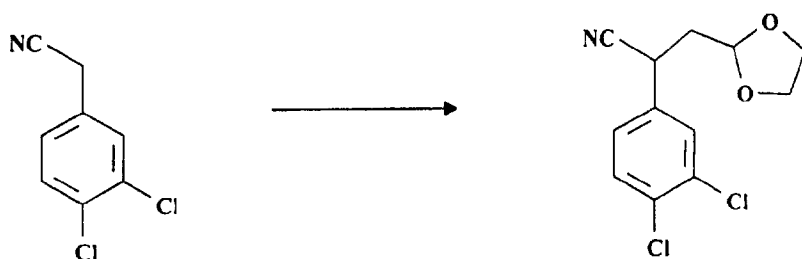
Found: C, 54.82; H, 5.85; N, 3.82. $\text{C}_{33}\text{H}_{39}\text{Cl}_3\text{F}_6\text{N}_2\text{O}$. 1.0 mol. water requires C,
15 55.20; H, 5.76; N, 3.90%.

The following Preparations illustrate the syntheses of certain of the starting materials used in the preceding Examples.

5

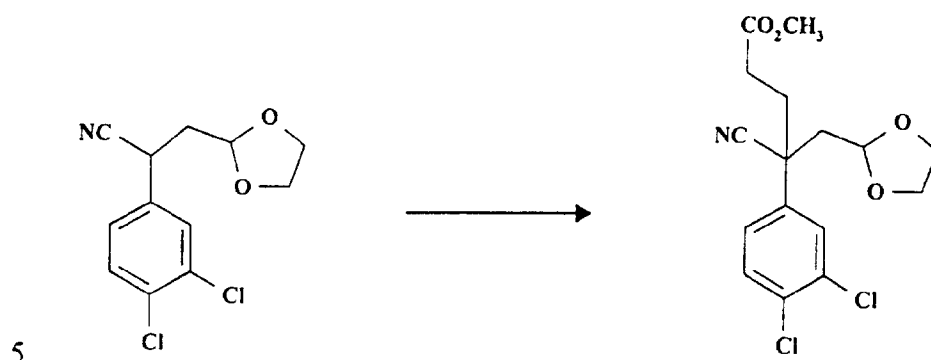
PREPARATION 1

2-(3,4-Dichlorophenyl)-3-(1,3-dioxolan-2-yl)propanenitrile



Sodium hydride (60% w/w dispersion in mineral oil) (4.73g) was suspended in
10 tetrahydrofuran (70ml) under a nitrogen atmosphere and the mixture cooled in
an ice-bath. A solution of 3,4-dichlorophenylacetonitrile (20g) in tetrahydrofuran
(80ml) was added dropwise over 35 minutes. The mixture was allowed to warm
to room temperature and stirred for 16 hours. 2-Bromomethyl-1,3-dioxolane
(19.71g) and tetra-n-butylammonium iodide (2g) were added and the resulting
15 mixture was heated under reflux for 4 hours. The mixture was cooled and
partitioned between ethyl acetate and water. The organic layer was separated
and washed with brine. The organic solvents were removed under reduced
pressure to yield a brown oil which was chromatographed on silica using 80:20,
by volume, ethyl acetate : hexane as the eluent to yield the product as an
20 orange mobile oil. This oil was then dissolved in methanol, cooled in ice and a
precipitate formed which was filtered, washed with methanol and dried under
reduced pressure to yield the title compound (15.8g) as a white solid.

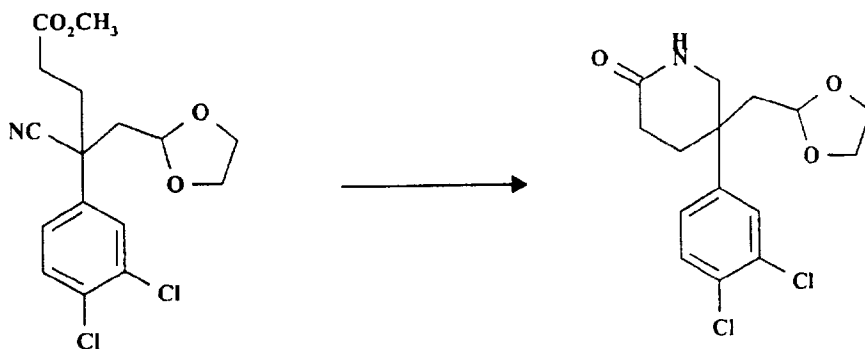
¹H-NMR (CDCl₃): δ = 7.40-7.50 (2H, m), 7.20-7.25 (1H, dd), 4.95 (1H, dd), 3.82-
25 4.05 (5H, m), 2.30-2.40 (1H, m), 2.05-2.15 (1H, m) ppm.

PREPARATION 2Methyl 4-cyano-4-(3,4-dichlorophenyl)-5-(1,3-dioxolan-2-yl)pentanoate

- The compound of Preparation 1 (5.0g) and methyl acrylate (1.77ml) were dissolved in methanol (15ml) and a 5% w/w methanolic solution of sodium methoxide (1.05ml) added. The mixture was heated at 40-50°C for 6 hours before adding additional 5% w/w methanolic sodium methoxide solution (0.5ml).
- 10 Heating was continued at 40-50°C for 15 hours, additional methyl acrylate (1.77ml) was added and heating continued for a further 4 hours. The mixture was cooled to room temperature and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane and washed twice with water. The organic layer was separated and dried over anhydrous magnesium
- 15 sulphate before removal of the solvent under reduced pressure to yield an oil which crystallised upon standing. The solid product was triturated with diethyl ether, filtered and dried to yield the title compound (4.7g) as a white solid.

- ¹H-NMR (CDCl₃): δ = 7.53 (1H, s), 7.48 (1H, d), 7.30 (1H, dd), 4.80 (1H, dd),
- 20 3.75-4.00 (4H, m), 3.63 (3H, s), 2.40-2.60 (2H, m), 2.05-2.34 (4H, m) ppm.

52

PREPARATION 35-(3,4-Dichlorophenyl)-5-(1,3-dioxolan-2-ylmethyl)-2(1H)-piperidinone

5

The compound of Preparation 2 (3.91g) was dissolved in glacial acetic acid (60ml) and platinum (II) oxide (0.35g) was added. The mixture was hydrogenated for 18 hours at 414kPa (60psi). The mixture was filtered through a short column of Arbacel (trade mark) filter aid and the filtrate was concentrated under reduced pressure to a thick oil. This was dissolved in ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate solution. The organic layer was separated and the solvent removed under reduced pressure until a white precipitate began to form. The precipitate was filtered and dried overnight under reduced pressure to the yield the title compound (3.01g) as a white solid.

10

15

¹H-NMR (CDCl₃): δ = 7.41 (2H, m), 7.19 (1H, dd), 6.2 (1H, s), 4.35 (1H, dd), 3.80-3.95 (4H, m), 3.65-3.75 (2H, m), 3.49 (1H, d), 2.35-2.42 (1H, m), 2.05-2.20 (3H, m), 1.85-1.92 (1H, m) ppm.

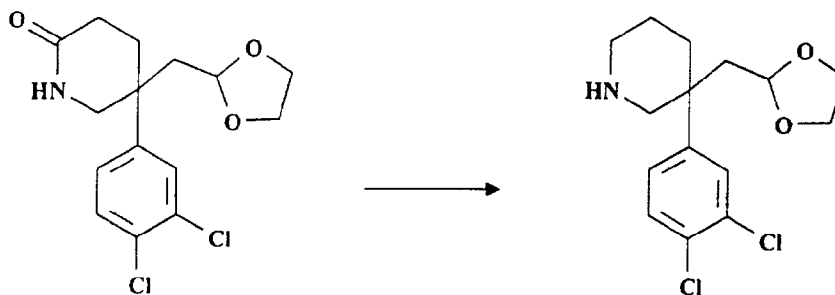
20

LRMS: m/z = 330 (m)⁺.

53

PREPARATION 43-(3,4-Dichlorophenyl)-3-(1,3-dioxolan-2-ylmethyl)piperidine

5



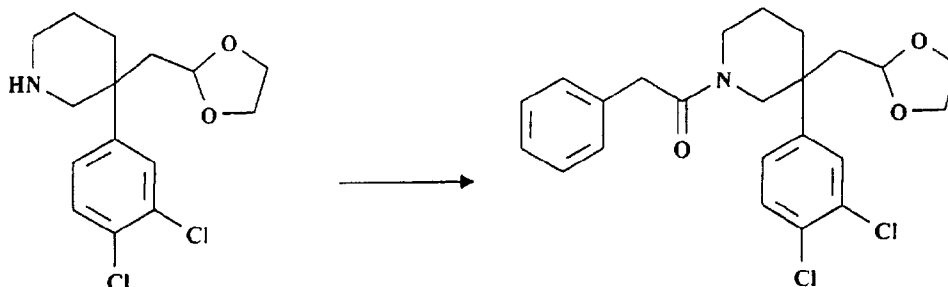
The compound of Preparation 3 (12g) was added portionwise to a solution of lithium aluminium hydride in anhydrous tetrahydrofuran (76ml of a 1M solution in tetrahydrofuran) and the mixture stirred at room temperature under a nitrogen atmosphere for 18 hours. Water (2.88ml) was carefully added over 20 minutes, the mixture was stirred for a further 15 minutes and 2N aqueous sodium hydroxide solution (2.88ml) added followed by water (8.6ml). The mixture was stirred for 1 hour and partitioned between diethyl ether and saturated aqueous sodium hydrogen carbonate solution. The organic phase was separated, dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure. The crude product was chromatographed on silica eluting with a solvent gradient of 95:5 changing to 90:10, by volume, dichloromethane : methanol to give the title compound (8g) as a yellow oil.

$^1\text{H-NMR}$ (CDCl_3): δ = 7.48 (1H, s), 7.39 (1H, d), 7.22 (1H, dd), 4.35 (1H, t), 3.86 (2H, m), 3.68 (2H, m), 3.30 (1H, d), 2.96 (1H, d), 2.79 (2H, m), 2.10 (1H, m), 1.95 (2H, m), 1.80-1.85 (1H, m), 1.40-1.65 (2H, m) ppm.

LRMS: m/z = 316 (m) $^+$.

25

54

PREPARATION 53-(3,4-Dichlorophenyl)-3-(1,3-dioxolan-2-ylmethyl)-1-phenylacetyl piperidine

5

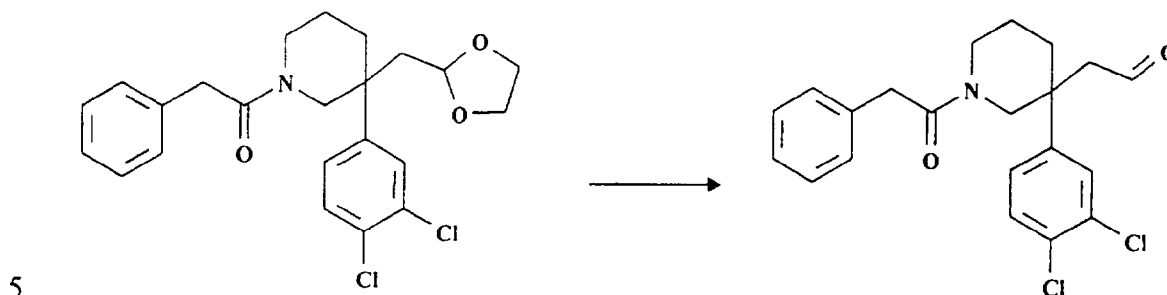
The compound of Preparation 4 (0.75g) and triethylamine (0.49ml) were dissolved in dichloromethane (20ml), the solution cooled in an ice-bath and phenylacetyl chloride (0.38ml) added dropwise. The mixture was stirred at room temperature for 1.5 hours and dichloromethane (25ml) added. The solution was

10 washed with water, the organic phase separated, dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure. The crude product was chromatographed on silica eluting with 2% v/v methanol in dichloromethane to give the title compound (0.75g) as a colourless oil.

15 ¹H-NMR (CDCl₃): δ = 7.49 (1H, s), 7.25-7.39 (2H, m), 7.10-7.15 (3H, m), 7.02 (2H, m), 4.83 (1H, d), 4.40 (1H, t), 3.80-3.95 (2H, m), 3.65-3.70 (4H, m), 3.58 (1H, m), 3.00-3.16 (2H, m), 2.15 (1H, m), 1.60-1.85 (3H, m), 1.39 (1H, m), 1.10 (1H, m) ppm.

20 LRMS: m/z = 434 (m)⁺.

55

PREPARATION 63-(3,4-Dichlorophenyl)-3-(formylmethyl)-1-phenylacetyl piperidine

The compound of Preparation 5 (0.75g) was dissolved in tetrahydrofuran (8ml), cooled in an ice-bath and 5N aqueous hydrochloric acid solution (14ml)

10 carefully added. The resulting mixture was stirred at room temperature for 18 hours and the solvent removed under reduced pressure to give a residue. The residue was dissolved in dichloromethane, washed with water and the organic phase dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure to give the title compound (0.66g) as a pale yellow oil.

15

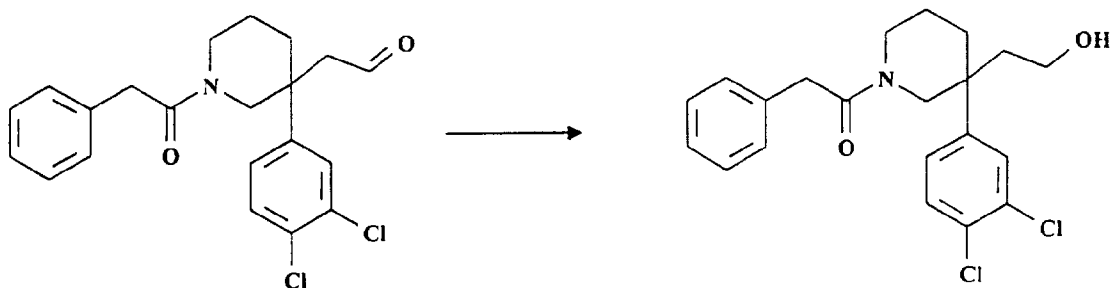
$^1\text{H-NMR}$ (CDCl_3): δ = 9.45 (1H, s), 7.10-7.49 (8H, m), 4.23 (1H, d), 3.60-3.38 (3H, m), 3.30-3.50 (2H, m), 2.50-2.66 (2H, q), 2.15 (1H, m), 1.90 (1H, m), 1.40 (1H, m), 1.30 (1H, m) ppm.

20 LRMS: m/z = 390 (m) $^+$.

56

PREPARATION 73-(3,4-Dichlorophenyl)-3-(2-hydroxyethyl)-1-phenylacetylpiperidine

5



Sodium borohydride (0.097g) was added to a solution of the compound of Preparation 6 (0.66g) in ethanol (15ml) and the mixture stirred at room temperature for 1 hour. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate. The mixture was acidified to pH 1 by the addition of 2N aqueous hydrochloric acid solution and then basified to pH 7 by the addition of solid sodium carbonate. The organic phase was separated, dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure. The crude product was chromatographed on silica eluting with 2.5% v/v methanol in dichloromethane to give the title compound (0.4g) as a colourless oil.

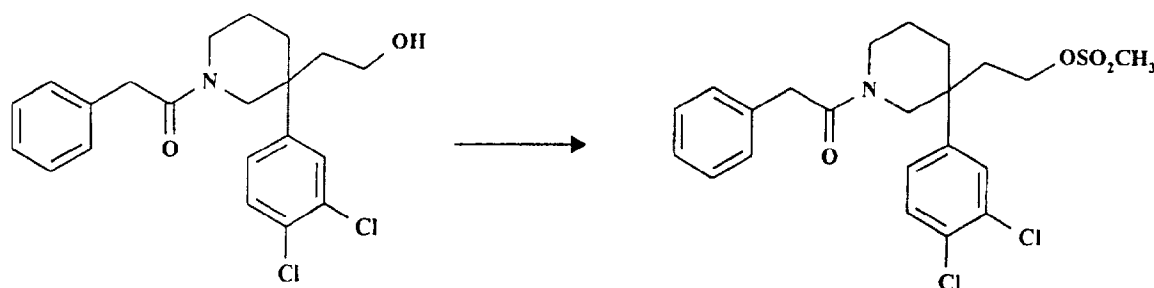
$^1\text{H-NMR}$ (CDCl_3): δ = 7.05-7.43 (8H, m), 4.27 (1H, d), 3.30-3.82 (7H, m), 2.01 (1H, m), 1.63-1.89 (4H, m), 1.40 (1H, m), 1.20 (1H, m) ppm.

LRMS: m/z = 392 (m) $^+$.

57

PREPARATION 83-(3,4-Dichlorophenyl)-3-(2-methanesulphonyloxyethyl)-1-phenylacetyl-
piperidine

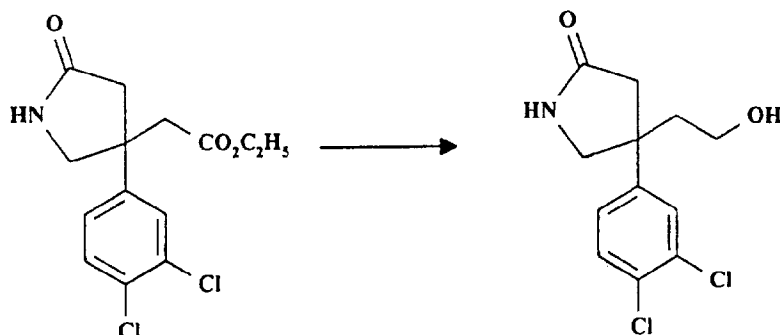
5



The compound of Preparation 7 (0.4g) and triethylamine (0.18ml) were
10 dissolved in dichloromethane (10ml), cooled in an ice-bath and
methanesulphonyl chloride (0.09ml) added. The mixture was stirred at room
temperature for 1 hour, dichloromethane (10ml) added and the solution washed
twice with water. The organic phase was dried over anhydrous magnesium
sulphate and the solvent removed under reduced pressure. The residue was
15 dissolved in acetonitrile and the solvent again removed under reduced pressure
to give the title compound (0.47g) as an oil.

¹H-NMR (CDCl₃): δ = 7.05-7.43 (8H, m), 4.30 (1H, d), 4.00 (1H, m), 3.90 (1H,
m), 3.70 (2H, m), 3.30-3.50 (3H, m), 2.91 (3H, s), 2.09 (1H, m), 2.00 (2H, m),
20 1.80 (1H, m), 1.42 (1H, m), 1.21 (1H, m) ppm.

58

PREPARATION 94-(3,4-Dichlorophenyl)-4-(2-hydroxyethyl)-2(1H)-pyrrolidinone

5

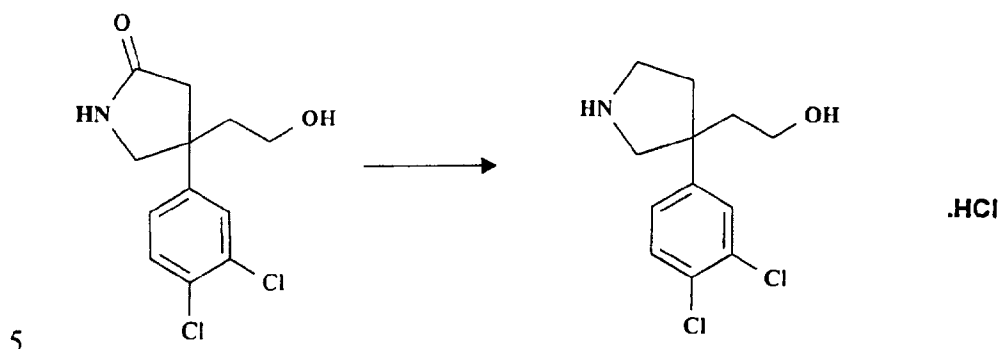
4-(3,4-Dichlorophenyl)-4-ethoxycarbonylmethyl-2(1H)-pyrrolidinone (4.8g) (see WO 94/26735) was dissolved in anhydrous tetrahydrofuran (50ml) and added, over 30 minutes, to a slurry of lithium aluminium hydride (0.6g) in anhydrous tetrahydrofuran (10ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 2 hours, further lithium aluminium hydride (0.3g) was added and stirring continued for 2.5 hours. Water (1.1ml) was carefully added, followed by 2N aqueous sodium hydroxide solution (1.1ml), water (2.2ml) and tetrahydrofuran (100ml). The mixture was stirred for 30 minutes and the resulting suspension filtered through a short column of Arbacel (trade mark) filter aid. The filtrate was collected and the solvent removed under reduced pressure to give a residue which was dissolved in dichloromethane and the solvent again removed under reduced pressure. The crude product was chromatographed on silica eluting with a solvent gradient of 96:4 changing to 90:10, by volume, dichloromethane:methanol to give the title compound (3.15g) as a gum.

20

¹H-NMR (CDCl₃): δ = 7.42 (1H, d), 7.29 (1H, s), 7.03 (1H, d), 6.04 (1H, s), 3.74 (1H, d), 3.63 (1H, d), 3.45-3.60 (2H, m), 2.71 (2H, s), 2.03-2.12 (2H, m), 1.57 (1H, t) ppm.

25

PREPARATION 10

3-(3,4-Dichlorophenyl)-3-(2-hydroxyethyl)pyrrolidine hydrochloride

A solution of diborane (1M solution in tetrahydrofuran; 300ml) was added to the compound of Preparation 9 (2.5g) and the mixture heated under reflux under a nitrogen atmosphere for 18 hours. The solution was cooled and carefully added to 6N aqueous hydrochloric acid solution (60ml) which had been pre-cooled in an ice-bath. The mixture was stirred at 0°C for 10 minutes and the pH adjusted to pH 14 by careful addition of sodium hydroxide pellets. Water (50ml) was added and the phases separated. A precipitate was in the lower aqueous phase. The organic layer was decanted and the aqueous layer extracted with tetrahydrofuran. The organic phases were combined and the solvent removed under reduced pressure. The crude product was dissolved in diethyl ether and filtered. Diethyl ether, saturated with hydrogen chloride gas, was added to the filtrate and a hazy solution formed. The solution was extracted twice with water (30ml, 10ml), the aqueous extracts combined and the water removed under reduced pressure. The product was dried under reduced pressure in the presence of phosphorus pentoxide to give the title compound (2.2g) as a white foam.

10

15

20

¹H-NMR (d₆-DMSO): δ = 7.63 (1H, d), 7.58 (1H, s), 7.33 (1H, d), 3.00-3.50 (6H, m), 2.26 (2H, m), 1.89 (2H, m) ppm.

PREPARATION 113,4,5-Trimethoxybenzoyl chloride

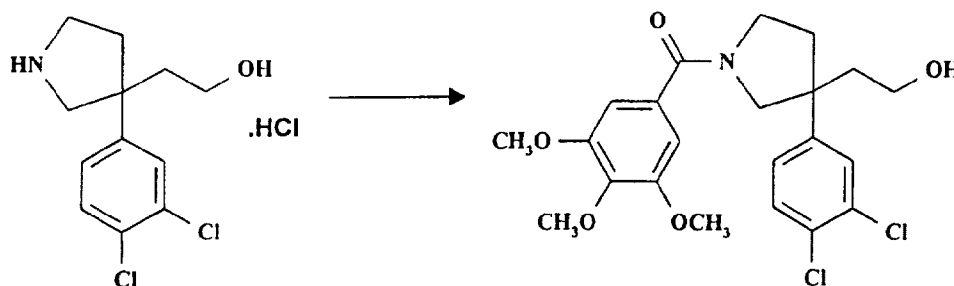
3,4,5-Trimethoxybenzoic acid (15g) was suspended in anhydrous
5 dichloromethane (150ml) and oxalyl chloride (13.5g) added, followed by
addition of catalytic dimethylformamide (3 drops). The mixture was stirred at
room temperature for 2.5 hours, additional dimethylformamide (2 drops) was
added and stirring continued for a further hour. The solvent was removed under
reduced pressure, the residue dissolved in dichloromethane and the solvent
10 removed under reduced pressure. The residue was again dissolved in
dichloromethane and the solvent removed under reduced pressure to give
3,4,5-trimethoxybenzoyl chloride (16.4g) as a white solid.

61

PREPARATION 12

3-(3,4-Dichlorophenyl)-3-(2-hydroxyethyl)-1-(3,4,5-trimethoxybenzoyl)-
pyrrolidine

5

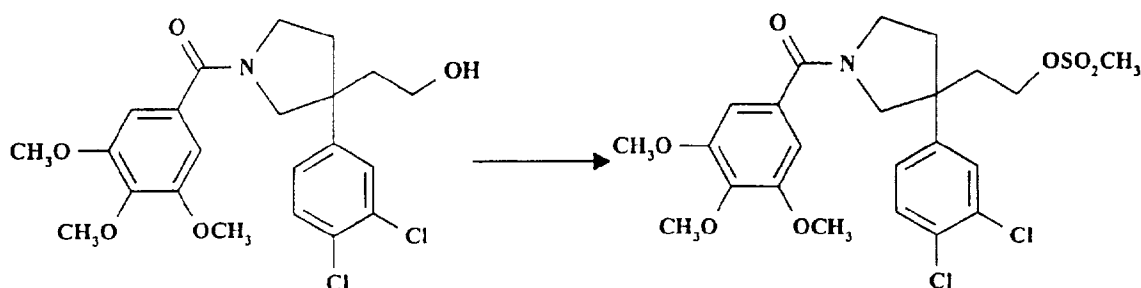


The compound of Preparation 10 (2.2 g) and triethylamine (4g) were dissolved in dichloromethane (60ml), the solution cooled in an ice-bath and a solution of 3,4,5-trimethoxybenzoyl chloride (4.8g) (see Preparation 11) in dichloromethane (40ml) added. The mixture was stirred at 0°C for 15 minutes, then at room temperature for 30 minutes before adding dichloromethane (100ml). The solution was washed sequentially with water (2x 50ml) and brine (50ml). The solvent was removed from the organic layer under reduced pressure. The resultant residue was dissolved in ethanol (100ml), 2N aqueous sodium hydroxide solution (15ml) added and the mixture stirred at room temperature for 1 hour. The ethanol was removed under reduced pressure to give a residue which was dissolved in dichloromethane and washed sequentially with water, 1N aqueous sodium hydroxide solution and brine. The organic layer was collected and the solvent removed under reduced pressure. The crude product was chromatographed on silica eluting with 98:2:0.1, by volume, dichloromethane: methanol: 0.88 aqueous ammonia solution to give the title compound (2.53g) as a white foam.

¹H-NMR (CDCl₃): δ = 7.00-7.50 (3H, m), 6.71 (2H, d), 3.30-4.10 (16H, m), 1.85-2.35 (4H, m) ppm.

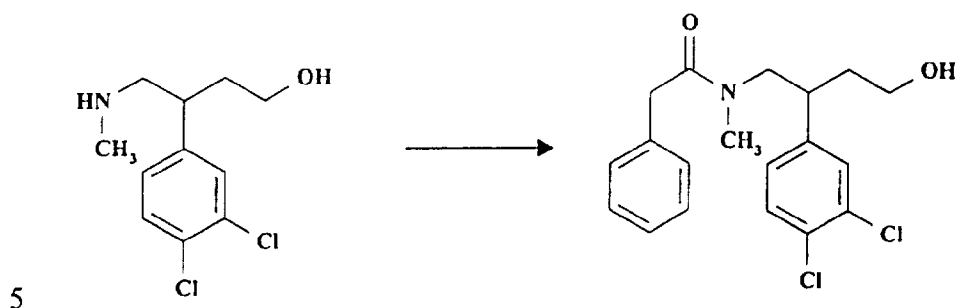
PREPARATION 133-(3,4-Dichlorophenyl)-3-(2-methanesulphonyloxyethyl)-1-(3,4,5-trimethoxybenzoyl)pyrrolidine

5



The compound of Preparation 12 (0.6g) and triethylamine (0.17g) were dissolved in dichloromethane (10ml), cooled in an ice-bath and
10 methanesulphonyl chloride (0.16g) added. The mixture was stirred for 100 minutes, dichloromethane (20ml) added and the solution washed sequentially with water (x2) and brine. The organic phase was dried over anhydrous sodium sulphate and the solvent removed under reduced pressure. The residue was
15 dissolved in acetonitrile and the solvent removed under reduced pressure to give the title compound (0.74g) as an oil.

$^1\text{H-NMR}$ (CDCl_3): δ = 6.99-7.50 (3H m), 6.72 (2H, d), 3.42-4.07 (15H, m), 2.83 (1.5H, s), 2.94 (1.5H, s), 2.06-2.40 (4H, m) ppm.

PREPARATION 143-(3,4-Dichlorophenyl)-4-(N-methylphenylacetamido)butan-1-ol

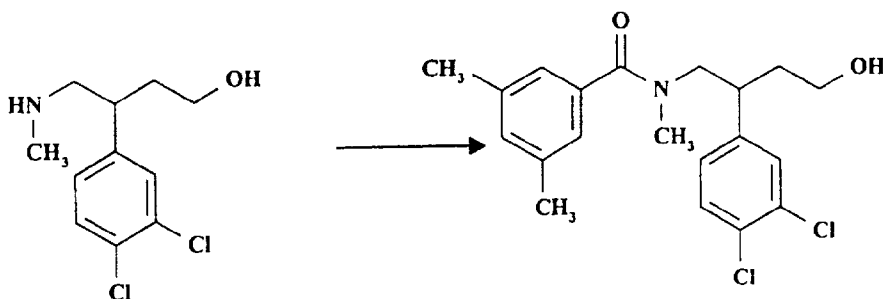
3-(3,4-Dichlorophenyl)-4-(N-methylamino)butan-1-ol (2g) (see EP-A-0474561) and triethylamine (0.9g) were dissolved in dichloromethane (20ml), the solution cooled in an ice-bath and a solution of phenylacetyl chloride (1.25g) in dichloromethane (5ml) added, dropwise over 10 minutes. The mixture was stirred at room temperature for 90 minutes and dichloromethane (25ml) added. The solution was washed sequentially with 2N aqueous hydrochloric acid solution (20ml) and brine (20ml). The dichloromethane was removed under reduced pressure and the crude product chromatographed on silica eluting with 98:2:0.1, by volume, dichloromethane:methanol : 0.88 aqueous ammonia solution to give the title compound (1.35g) as a gum.

15

¹H-NMR (CDCl₃): δ = 7.21-7.33 (5H, m), 7.09 (2H, d), 6.99 (1H, dd), 3.79 (1H, dd), 3.62 (2H, s), 3.38-3.53 (3H, m), 3.15 (1H, m), 2.72 (3H, s), 1.60-1.90 (3H, m) ppm.

20

PREPARATION 15

3-(3,4-Dichlorophenyl)-4-(N-methyl-3,5-dimethylbenzamido)butan-1-ol

5

3-(3,4-Dichlorophenyl)-4-(N-methylamino)butan-1-ol (see EP-A-0474561) (0.75g) and triethylamine (1.2g) were dissolved in dichloromethane (20ml), the solution cooled in an ice-bath and a solution of 3,5-dimethylbenzoyl chloride (1.5g) added dropwise. The mixture was stirred at room temperature for 18 hours and dichloromethane (50ml) added. The solution was washed with water (3x 50ml) and the solvent removed under reduced pressure. The resultant residue was dissolved in methanol (25ml), 2N aqueous sodium hydroxide solution (6ml) added and the mixture stirred at room temperature for 18 hours.

15 The methanol was removed under reduced pressure, water (20ml) was added and the solution extracted with dichloromethane (2x 25ml). The organic phases were combined and the solvent removed under reduced pressure. The crude product was chromatographed on silica eluting with 2.5% v/v methanol in dichloromethane to give the title compound (0.68g) as a foam.

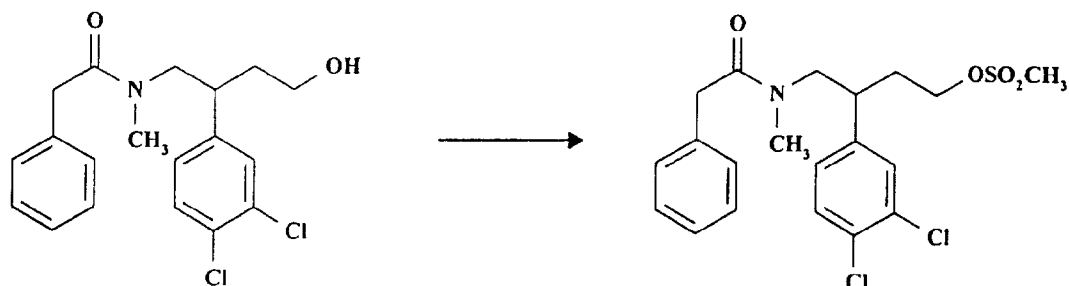
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$^1\text{H-NMR}$ (CDCl_3): δ = 6.7-7.45 (6H, m), 2.60-4.00 (8H, m), 2.31 (6H, s), 1.75-2.09 (2H, m) ppm.

65

PREPARATION 163-(3,4-Dichlorophenyl)-1-methanesulphonyloxy-4-(N-methylphenylacetamido)-
butane

5



The compound of Preparation 14 (1.35g) and triethylamine (0.56g) were dissolved in dichloromethane (15ml), cooled in an ice-bath and
 10 methanesulphonyl chloride (0.50g) added. The mixture was stirred for 30 minutes, dichloromethane (35ml) added and the solution washed sequentially with water (2x 30ml) and brine (30ml). The organic phase was dried over anhydrous sodium sulphate and the solvent removed under reduced pressure. The residue was dissolved in acetonitrile and the solvent removed under
 15 reduced pressure to give the title compound (1.57g) as an oil.

$^1\text{H-NMR}$ (CDCl_3): δ = 7.15-7.35 (5H, m), 7.09 (2H, d), 7.01 (1H, dd), 4.15 (1H, m), 3.96 (1H, m), 3.72 (1H, dd), 3.62 (2H, s), 3.54 (1H, m), 3.14 (1H, m), 2.93 (3H, s), 2.77 (3H, s), 2.12 (1H, m), 1.95 (1H, m) ppm.

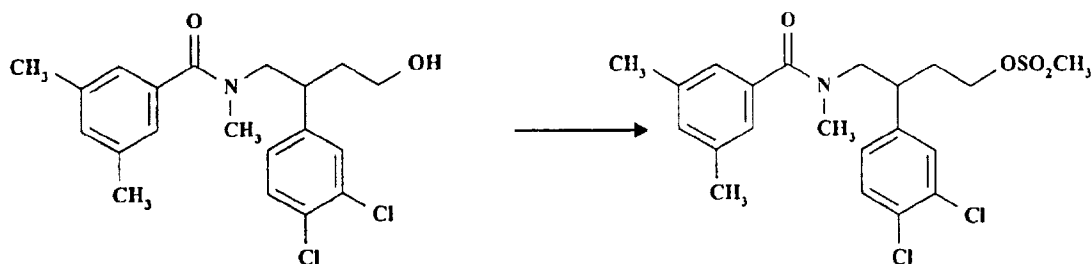
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PREPARATION 17

3-(3,4-Dichlorophenyl)-1-methanesulphonyloxy-4-(N-methyl-3,5-
dimethylbenzamido)butane

5

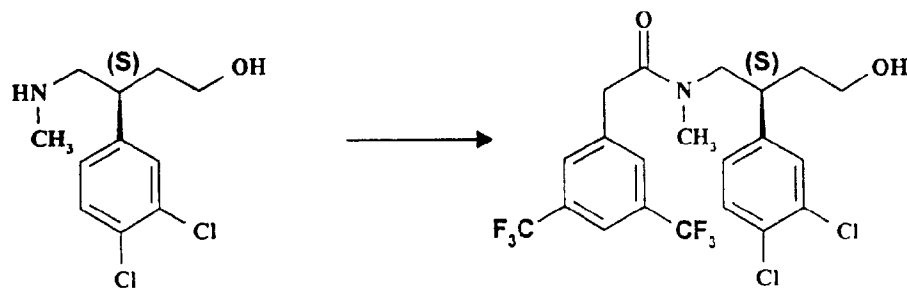


The title compound was prepared in an analogous fashion to the compound of Preparation 16 using the compound of Preparation 15 as the starting material.

- 10 $^1\text{H-NMR}$ (CDCl_3): δ = 7.05-7.46 (3H, m), 7.00 (1H, s), 6.73 (2H, s), 3.80-4.30 (3H, m), 3.05-3.65 (3H, m), 2.94 (3H, s), 2.71 (2H, s), 2.20-2.38 (7H, m), 2.05 (1H, m) ppm.

PREPARATION 18

- 15 3(S)-(3,4-Dichlorophenyl)-4-(N-methyl-3,5-bis(trifluoromethyl)phenylacetamido)-
butan-1-ol



- 3(S)-(3,4-Dichlorophenyl)-4-(N-methylamino)butan-1-ol (2.5g) (see EP-A-0474561) and triethylamine (6g) were dissolved in dichloromethane (50ml), the
 20 solution cooled in an ice-bath and a solution of 3,5-bis(trifluoromethyl)-phenylacetyl chloride (9.2g) in dichloromethane (20ml) added, dropwise over 15

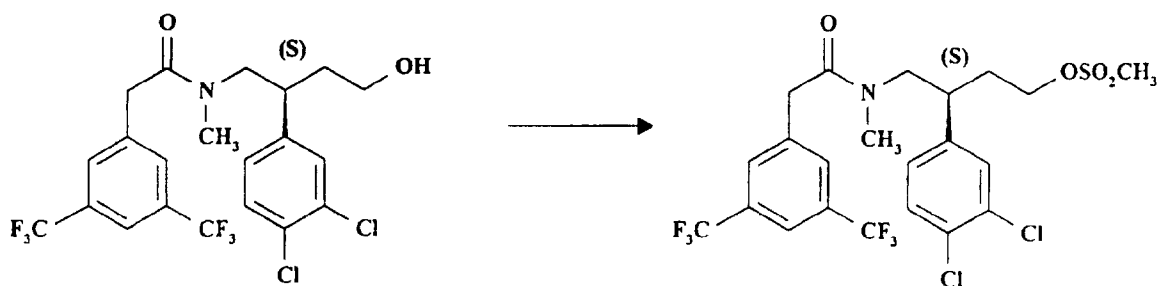
67

- minutes. The mixture was stirred at room temperature for 1 hour and dichloromethane (100ml) added. The solution was washed sequentially with water (50ml), 2N aqueous hydrochloric acid solution (2x 50ml) and water (50ml)
- 5 before removal of the dichloromethane under reduced pressure. The resultant residue was dissolved in ethanol (75ml), 2N aqueous sodium hydroxide solution (20ml) added and the mixture stirred at room temperature for 18 hours. The ethanol was removed under reduced pressure, water (50ml) was added and the solution extracted with dichloromethane (2x 50ml). The organic phases were
- 10 combined and the solvent removed under reduced pressure. The crude product was chromatographed on silica eluting with 96:4:0.25, by volume, dichloromethane:methanol: 0.88 aqueous ammonia solution to give the title compound (4.3g) as a yellow gum.
- 15 ¹H-NMR (CDCl₃): δ = 7.25-7.78 (5H, m), 7.03 (1H, d), 3.89 (1H, dd), 3.33-3.71 (5H, m), 3.20 (1H, m), 2.88 (0.5H, s,) 2.84 (2.5H, s) 1.70-1.90 (2H, m), 1.57 (1H, m) ppm (1:5 mixture of amide rotamers)
- LRMS: m/z = 502 (m)⁺.

20

PREPARATION 19

3(S)-(3,4-Dichlorophenyl)-1-methanesulphonyloxy-4-(N-methyl-3,5-
bis(trifluoromethyl)phenylacetamido)butane



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The compound of Preparation 18 (2.2g) and triethylamine (0.65g) were dissolved in dichloromethane (20ml), cooled in an ice-bath and methanesulphonyl chloride (0.55g) added. The mixture was stirred for 30 minutes, dichloromethane (50ml) added and the solution washed sequentially with water (x3) and brine. The organic phase was dried over anhydrous sodium sulphate and the solvent removed under reduced pressure. The residue was dissolved in acetonitrile and the solvent removed under reduced pressure to give the title compound (2.5g) as an oil.

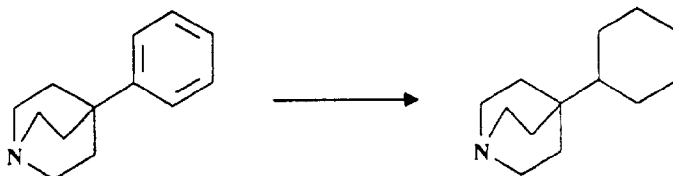
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$^1\text{H-NMR}$ (CDCl_3): δ = 7.79 (1H, s), 7.67 (2H, s), 7.39 (1H, d), 7.29 (1H, d), 7.06 (1H, dd), 4.18 (1H, m), 3.99 (1H, m), 3.87 (1H, dd), 3.71 (2H, s), 3.41 (1H, m), 3.19 (1H, m), 2.93 (3H, s), 2.89 (3H, s) 2.12 (1H, m), 1.95 (1H, m) ppm.

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PREPARATION 20

4-Cyclohexylquinuclidine



4-Phenylquinuclidine (5g, see J. Org. Chem., 1957, **22**, 1484) was dissolved in glacial acetic acid (25ml), 5% rhodium-on-alumina (2g) was added and the mixture hydrogenated for 5 days at 345kPa (50psi). The mixture was filtered through a short column of Arbocel (trade mark) filter aid and the residue washed with methanol. The filtrate was collected and the solvent removed under reduced pressure. The resultant residue was dissolved in water and the

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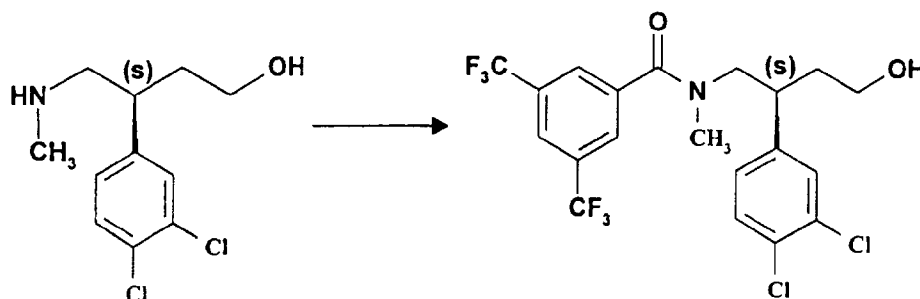
pH adjusted to >10 by addition of 0.88 aqueous ammonia solution. The aqueous mixture was extracted with ethyl acetate (x3), the organic layers combined, washed with brine, dried over anhydrous sodium sulphate and the solvent removed under reduced pressure to give 4-cyclohexylquinuclidine (4.7g) as a pale pink solid.

$^1\text{H-NMR}$ (CDCl_3): δ = 2.75-2.96 (6H, m), 1.60-1.85 (5H, m), 1.06-1.45 (9H, m), 1.80-1.98 (3H, m) ppm.

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PREPARATION 21

3(S)-(3,4-Dichlorophenyl)-4-(N-methyl-3,5-bis(trifluoromethyl)-benzamido)butan-1-ol



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(3S)-3-(3,4-Dichlorophenyl)-4-(N-methylamino)butan-1-ol (0.7g) (see EP-A-0474561) and triethylamine (1.1g) were dissolved in dichloromethane (20ml), the solution cooled in an ice bath and a solution of 3,5-bis(trifluoromethyl)-benzoyl chloride (2.3g) added, dropwise. The mixture was stirred at room temperature for 18 hours and dichloromethane (30ml) added. The solution was washed with water (3x 50ml) and the solvent removed under reduced pressure. The resultant residue was dissolved in methanol (30ml), 2N aqueous sodium

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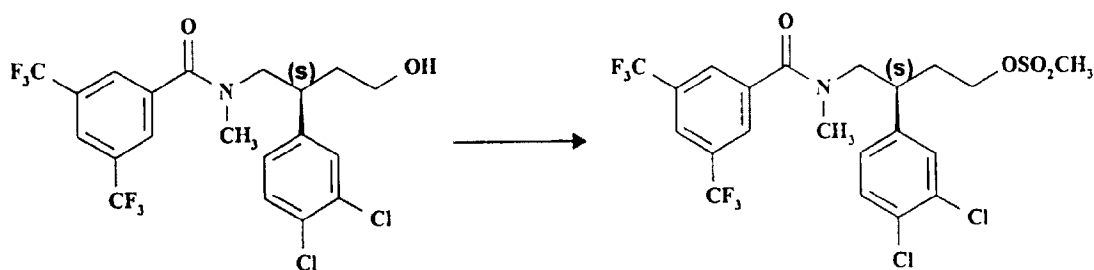
hydroxide solution (10ml) added and the mixture heated on a steam bath for 30 minutes. The methanol was removed under reduced pressure, water (20ml) was added and the solution extracted with diethyl ether (50ml). The organic phase was collected and washed with 2N aqueous sodium hydroxide solution (2x 20ml). The organic phase was collected and the solvent removed under reduced pressure to give a residue which was dissolved in dichloromethane and the solvent removed under reduced pressure. The crude product was chromatographed on silica gel eluting with 2.5%, by volume, methanol/
 10 dichloromethane to give the title compound (0.55g) as a foam.

$^1\text{H-NMR}$ (CDCl_3): δ = 7.88 (1H,s), 7.59 (2H,s), 7.35-7.45 (2H,m), 7.19 (1H,m), 3.00-3.95 (5H,m), 2.71 (3H,s), 1.80-2.05 (2H,m), 1.61 (1H,s) ppm.

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PREPARATION 22

3(S)-(3,4-Dichlorophenyl)-1-methanesulphonyloxy-4-(N-methyl-3,5-bis(trifluoromethyl)benzamido)butane



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The title compound was prepared in an analogous fashion to the compound of Preparation 19 using the compound of Preparation 21 as the starting material.

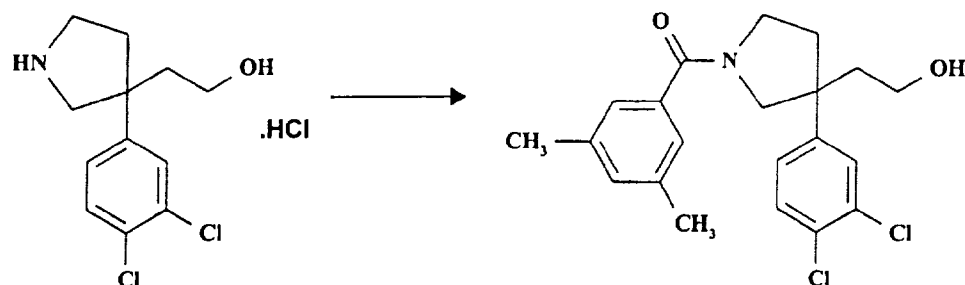
71

$^1\text{H-NMR}$ (CDCl_3): δ = 7.90 (1H,s), 7.61 (2H,s), 7.35-7.48 (2H,m), 7.19 (1H,m), 4.26 (1H,m), 3.60-4.10 (3H,m), 3.37 (1H,m), 2.95 (3H,s), 2.78 (3H,s), 2.25 (1H,m), 2.05 (1H,m) ppm.

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PREPARATION 23

3-(3,4-Dichlorophenyl)-3-(2-hydroxyethyl)-1-(3,5-dimethylbenzoyl)pyrrolidine



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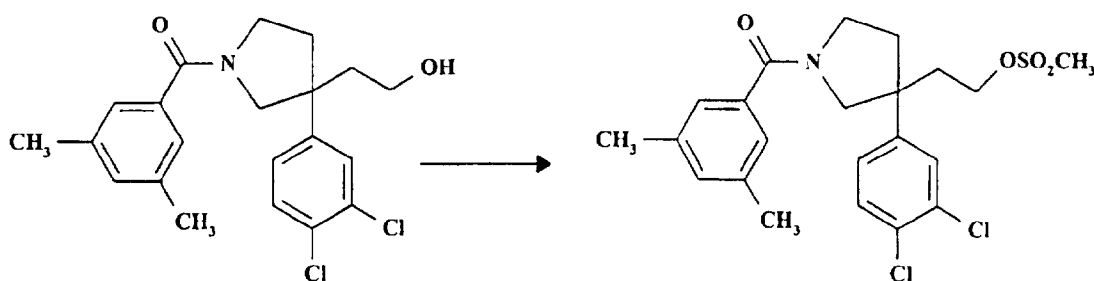
The title compound was prepared in an analogous fashion to the compound of Preparation 12 using the compound of Preparation 10 and 3,5-dimethylbenzoyl chloride as starting materials.

15 $^1\text{H-NMR}$ (CDCl_3): δ = 6.95-7.50 (6H,m), 3.30-4.05 (7H,m), 1.83-2.40 (10H,m) ppm.

72

PREPARATION 243-(3,4-Dichlorophenyl)-3-(2-methanesulphonyloxyethyl)-1-(3,5-dimethylbenzoyl)pyrrolidine

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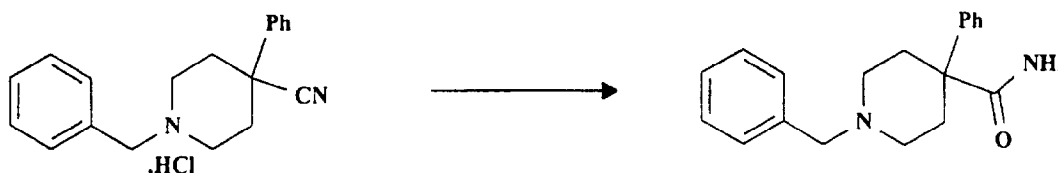


The title compound was prepared in an analogous fashion to the compound of Preparation 13 using the compound of Preparation 23 as the starting material.

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$^1\text{H-NMR}$ (CDCl_3): δ = 6.99-7.50 (6H,m), 3.37-4.06 (6H,m), 2.92 (1.5H,s), 2.80 (1.5H,s), 2.05-2.40 (10H,m) ppm.

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PREPARATION 251-Benzyl-4-carbamoyl-4-phenylpiperidine

1-Benzyl-4-cyano-4-phenylpiperidine hydrochloride (10g) was carefully added to concentrated sulphuric acid (50ml) (cooled in an ice-bath) over 15 minutes and the resulting solution left to stand at room temperature for 20 hours. The solution was added to ice (200g) and the aqueous mixture basified ($\text{pH} > 10$) by addition of 0.880 aqueous ammonia solution and then extracted with ethyl

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acetate (3x 100ml). The organic phases were combined, dried over anhydrous sodium sulphate and the solvent removed under reduced pressure to give a residue which was chromatographed on silica gel eluting with 5:95, by volume, methanol: ethyl acetate to give the title compound (8.6g) as an oil.

$^1\text{H-NMR}$ (CDCl_3): δ = 7.20-7.42 (10H, m), 5.15 (2H, s), 3.48 (2H, s), 2.35-2.65 (6H, m), 2.05-2.15 (2H, m) ppm.

LRMS m/z = 295 ($m+1$)⁺

PREPARATION 26

1-Benzyl-4-methoxycarbonyl-4-phenylpiperidine

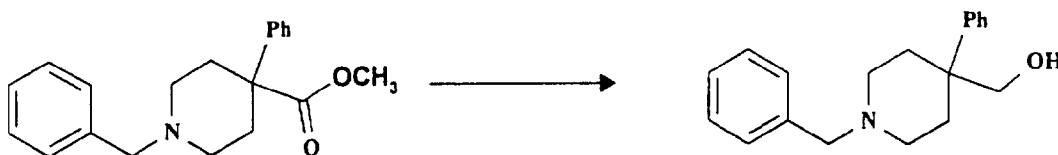


The compound of Preparation 25 (7g) was dissolved in methanol (150ml) and the solution saturated with hydrogen chloride gas. The mixture was left to stand at room temperature for 7 hours. Methanol (150ml) was then added and a continuous stream of hydrogen chloride gas bubbled through the solution whilst heating under reflux for a further 3 hours. The mixture was cooled and left to stand at room temperature for 16 hours. The solvent was removed under reduced pressure. The residue was dissolved in water, basified ($\text{pH} > 10$) by addition of solid sodium carbonate and extracted with ethyl acetate (x3). The organic phases were combined and the solvent removed under reduced pressure to give the crude product which was chromatographed on silica gel eluting with ethyl acetate to yield the title compound (2.9g) as a white solid.

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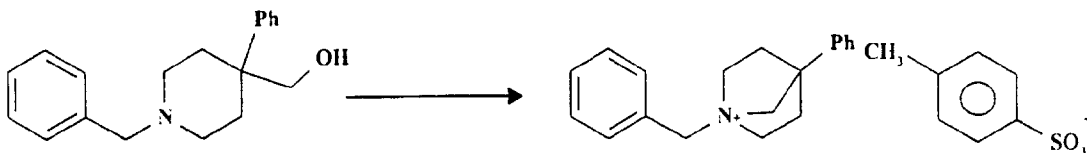
$^1\text{H-NMR}$ (CDCl_3): δ = 7.19-7.40 (10H, m), 3.63 (3H, s), 3.47 (2H, s), 2.80 (2H, m), 2.55 (2H, m), 2.20 (2H, m), 2.00 (2H, m) ppm.

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PREPARATION 271-Benzyl-4-hydroxymethyl-4-phenylpiperidine

The compound of Preparation 26 (2.7g) was dissolved in anhydrous diethyl ether (50ml) and lithium aluminium hydride (0.33g) added in 4 portions over 2 minutes. The mixture was stirred at room temperature for 30 minutes, water (0.4ml) was carefully added followed by 2N aqueous sodium hydroxide solution (0.4ml) and further water (0.8ml). The mixture was stirred and the resulting granular precipitate removed by filtration. The solvent was removed from the filtrate under reduced pressure to give a solid which was dissolved in dichloromethane, dried over anhydrous sodium sulphate and the solvent again removed under reduced pressure to yield the title compound (2.4g) as a white solid.

$^1\text{H-NMR}$ (CDCl_3): δ = 7.20-7.40 (10H, m), 3.60 (2H, d), 3.42 (2H, s), 2.60 (2H, m), 2.10-2.32 (4H, m), 1.90-2.00 (2H, m) ppm.

PREPARATION 281-Benzyl-4-phenyl-1-azoniabicyclo[2.2.1]heptane 4-methylphenylsulphonate

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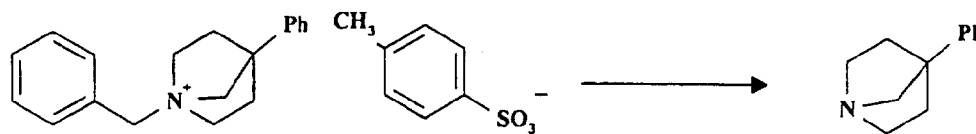
75

The compound of Preparation 27 (2.3g) was dissolved in pyridine (20ml) and cooled in an ice-bath before addition of 4-methylphenylsulphonyl chloride (1.7g). The mixture was left at 0°C for 16 hours before removal of the solvent under reduced pressure. The residue was suspended in 10% aqueous potassium carbonate solution (40ml) and extracted with toluene (3x50ml). The combined organic phases were stirred with anhydrous potassium carbonate for 10 minutes and filtered. The filtrate was collected and the volume reduced to about 40ml by evaporation under reduced pressure. The solution was then heated at 90°C for 7 hours, left to stand at room temperature for 16 hours and the resulting precipitate filtered off. The precipitate was washed with diethyl ether and dried to yield the title compound (2.75g) as a white solid.

¹H-NMR (CDCl₃): δ = 7.84 (2H, d), 7.60 (2H, d), 7.10-7.40 (10H, m), 5.11 (2H, s), 4.05-4.15 (2H, m), 3.92 (2H, s), 3.60-3.70 (2H, m), 2.30-2.42 (5H, m), 2.05-2.15 (2H, m) ppm.

PREPARATION 29

4-Phenyl-1-azabicyclo[2.2.1]heptane



The compound of Preparation 28 (2.7g) was dissolved in methanol (20ml), 10% w/w palladium-on-carbon (0.3g) was added and the mixture was hydrogenated for 18 hours at 207kPa (30psi). Additional 10% w/w palladium-on-carbon was added (0.2g) and the mixture hydrogenated for a further 24 hours. The mixture was then filtered through a short column of a filter aid (Arbacel, trade mark).

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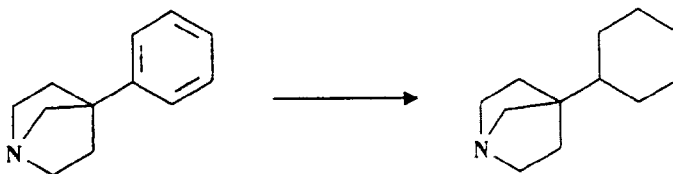
The solvent was removed from the filtrate under reduced pressure to give a residue which was dissolved in diethyl ether. The solvent was again removed under reduced pressure. The residue was dissolved in diethyl ether (50ml), washed with 1N aqueous sodium hydroxide solution (25ml) and the aqueous phase extracted twice with diethyl ether. The organic phases were combined, the solvent was removed under reduced pressure, the residue dissolved in ethyl acetate and the solution dried over anhydrous sodium sulphate. The solvent was again removed under reduced pressure to yield the title compound (0.91g) as a solid.

$^1\text{H-NMR}$ (CDCl_3): δ = 7.18-7.38 (5H, m), 3.05-3.18 (2H, m), 2.68-2.80 (4H, m), 1.80-1.90 (2H, m), 1.60-1.70 (2H, m) ppm.

LRMS m/z = 174 ($m+1$)⁺

PREPARATION 30

4-Cyclohexyl-1-azabicyclo[2.2.1]heptane



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4-Phenyl-1-azabicyclo[2.2.1]heptane (0.62g) (see Preparation 29) was dissolved in glacial acetic acid (3ml), 5% w/w rhodium-on-alumina (0.1g) was added and the mixture hydrogenated for 7 days at 345kPa (50psi). 5% w/w Rhodium-on- alumina (0.05g) was added and the mixture hydrogenated at 345kPa (50psi) for a further 2 days. The mixture was filtered through a short

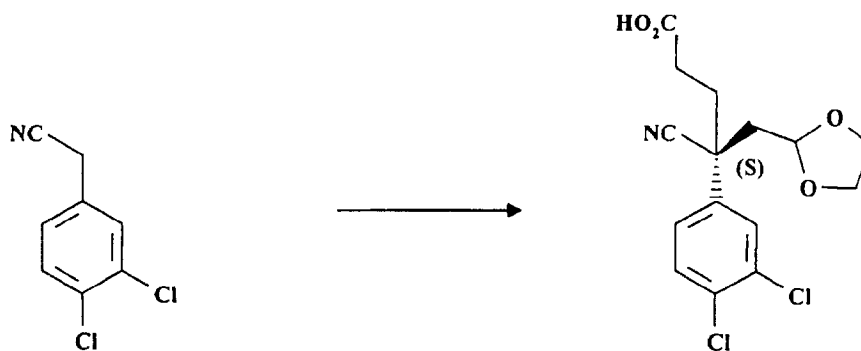
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column of filter aid (Arbacel, trade mark) and the residue washed with methanol. The filtrate was collected and the solvent removed under reduced pressure to give a residue. This was dissolved in water and the pH adjusted to
5 >10 by addition of 0.88 aqueous ammonia solution. The aqueous mixture was extracted with ethyl acetate (x3), the organic layers combined, washed with brine, dried over anhydrous sodium sulphate and the solvent removed under reduced pressure to give 4-cyclohexyl-1-azabicyclo[2.2.1]heptane (0.57g) as an oil.

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$^1\text{H-NMR}$ (CDCl_3): δ = 2.82-2.98 (2H, m), 2.50-2.68 (2H, m), 2.23 (2H, s), 1.02-1.80 (15H, m) ppm.

PREPARATION 31

15 (4S)-4-Cyano-4-(3,4-dichlorophenyl)-5-(1,3-dioxolan-2-yl)pentan-1-oic acid

To a 1.0M solution of lithium hexamethyldisilazide in tetrahydrofuran (4.69L) at 5°C under nitrogen was added a solution of 3,4-dichlorophenylacetonitrile
20 (750g) in tetrahydrofuran (750ml), dropwise, over 45 minutes. The reaction was stirred for 2 hours, cooled again to 5°C and a solution of 2-bromomethyl-1,3-dioxolane (782g) in tetrahydrofuran (780ml) added, dropwise, over 50 minutes.

Tetra-n-butylammonium iodide (75g) was then added portionwise, and the mixture allowed to warm to room temperature and stirred for 14 hours. The reaction was then cooled to 5°C and a 1.0M solution of lithium

5 hexamethyldisilazide in tetrahydrofuran (4.69L) added, dropwise. The mixture was stirred for 5 hours at room temperature. The solution was then cooled to 5°C and a solution of ethyl 3-bromopropanoate (840.5g) in tetrahydrofuran (840ml) added, dropwise, over 50 minutes. The reaction was allowed to stir for 14 hours. The reaction mixture was cooled to 5°C and 1.5M aqueous sodium

10 hydroxide solution (sufficient to contain 255g of sodium hydroxide) was added and the mixture stirred for 14 hours. Water (5L) was added and the mixture extracted with ethyl acetate (2 x 3L). The combined organic extracts were washed with water (2 x 5L). The aqueous phases were combined, acidified to pH1 using 5N aqueous hydrochloric acid solution and then extracted with ethyl

15 acetate (2 x 3L). The combined organic extracts were concentrated under reduced pressure to a concentration of approximately 3ml/g based on the theoretical yield of the product. The above experimental procedure was then repeated on a identical scale.

20 To the combined organic solutions from both reactions was added (S)-(-)-alpha-methylbenzylamine (1.13kg) and the mixture stirred for 14 hours. The thick slurry was then stirred with cooling in an ice-bath for 2 hours, filtered, the solid washed with ethyl acetate (2 x 1L) and dried under reduced pressure at 35°C to give 1.85kg of material. A portion of this material (1.34kg) was dissolved in a

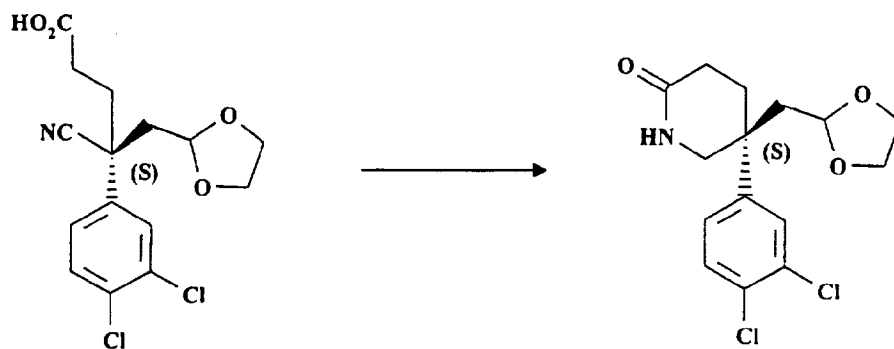
25 mixture of 2-butanone (2L) and water (503ml) and heated under reflux. A further portion of 2-butanone (4.7L) was added and the solution allowed to cool slowly to room temperature overnight. The resulting solid was filtered off, washed with 2-butanone (2 x 1L) and dried under reduced pressure at 35°C for 10 hours to give 563g of material (93.8% e.e by HPLC analysis). A further

recrystallisation from 2-butanone/water gave (4S)-4-cyano-4-(3,4-dichlorophenyl)-5-(1,3-dioxolan-2-yl)pentan-1-oic acid, (S)-(-)-alpha-methylbenzylamine salt in 99.8% e.e.. To a stirred solution of this salt in ethyl acetate and water was added 5N aqueous hydrochloric acid solution until pH1 was achieved. The mixture was stirred for 30 minutes, the layers separated and the aqueous phase extracted with ethyl acetate. The combined organic layers were washed with water and the solvent removed under reduced pressure to give (4S)-4-cyano-4-(3,4-dichlorophenyl)-5-(1,3-dioxolan-2-yl)pentan-1-oic acid.

¹H-NMR (CDCl₃): δ = 9.90 (1H, br. s), 7.25-7.55 (3H, m), 4.75-4.85 (1H, m), 3.70-4.00 (4H, m), 2.40-2.65 (2H, m), 2.05-2.35 (4H, m) ppm.

PREPARATION 32

(5S)-5-(3,4-Dichlorophenyl)-5-(1,3-dioxolan-2-ylmethyl)-2(1H)-piperidinone



To a solution of (4S)-4-cyano-4-(3,4-dichlorophenyl)-5-(1,3-dioxolan-2-yl)pentan-1-oic acid (13.5g) (see Preparation 31) in glacial acetic acid (130ml) was added platinum oxide (1.21g) and the mixture hydrogenated at 414kPa (60psi) and room temperature for 17 hours. The catalyst was removed by filtration and a further portion of platinum oxide (1.21g) added. The mixture was

80

then hydrogenated at 414kPa (60psi) and room temperature for a further 48 hours. The catalyst was removed by filtration and the solvent removed under reduced pressure. The residue was dissolved in ethyl acetate (80ml) and washed with saturated aqueous sodium bicarbonate solution (2 x 75ml). The organic phase was separated and the solvent removed under reduced pressure. The resulting solid was stirred in a solution of hexane (20ml) and ethyl acetate (20ml) for 2 hours at 0°C then filtered to give the title compound (8.15g) as a white solid.

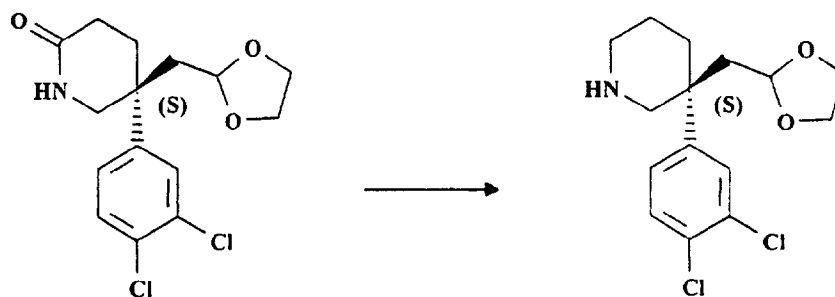
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¹H-NMR (CDCl₃): δ = 7.20-7.45 (3H, m), 6.15 (1H, br. s), 4.35-4.40 (1H, m), 3.80-3.90 (3H, m), 3.65-3.75 (2H, m), 3.45-3.55 (1H, m), 2.35-2.40 (1H, m), 2.00-2.25 (4H, m), 1.85-1.95 (1H, m) ppm.

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PREPARATION 33

(3S)-3-(3,4-Dichlorophenyl)-3-(1,3-dioxolan-2-ylmethyl)piperidine



20 The title compound was prepared by a similar method to that of Preparation 4 using the compound of Preparation 32 as the starting material.

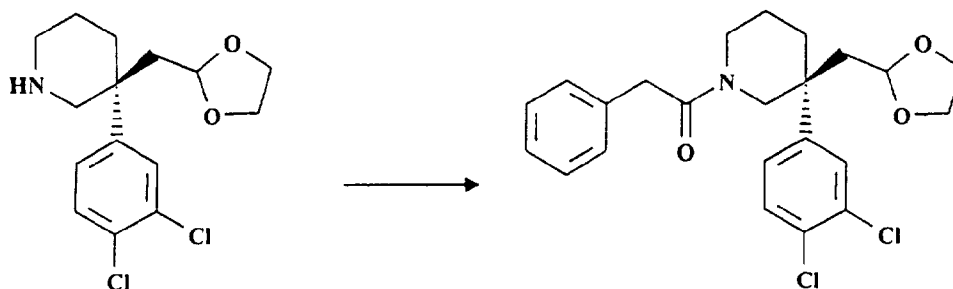
¹H-NMR: Identical to that for the compound of Preparation 4.

81

PREPARATION 34

(3S)-3-(3,4-Dichlorophenyl)-3-(1,3-dioxolan-2-ylmethyl)-1-phenylacetyl-
piperidine

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The title compound was prepared by an analogous method to that of Preparation 5 using the compound of Preparation 33 as the starting material.

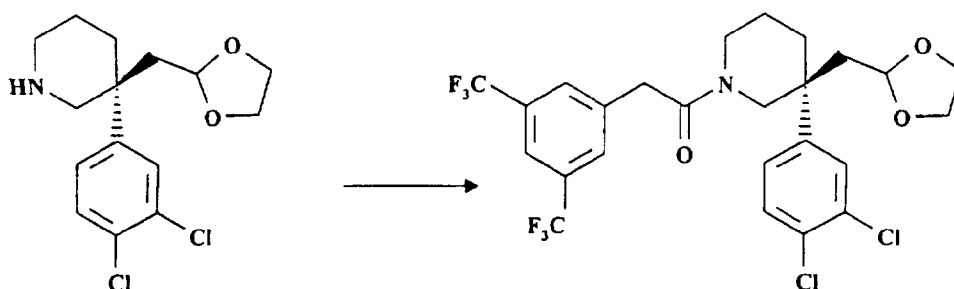
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¹H-NMR: Identical to that for the compound of Preparation 5.

PREPARATION 35

(3S)-1-(3,5-Bis(trifluoromethyl)phenylacetyl)-3-(3,4-dichlorophenyl)-3-(1,3-
dioxolan-2-ylmethyl)piperidine

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The compound of Preparation 33 (1.42g), 3,5-bis(trifluoromethyl)phenylacetic acid (1.11g) and 4-methylmorpholine N-oxide (1.34ml) were dissolved in dichloromethane (15ml) and 1-hydroxybenzotriazole monohydrate (0.62g)

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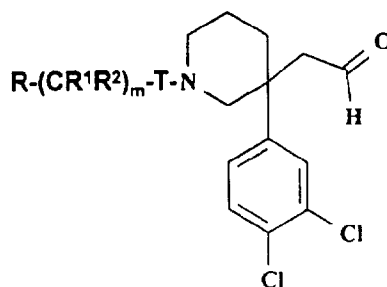
added, followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.86g). The mixture was stirred at room temperature for 18 hours and the solvent then removed under reduced pressure. The residue was dissolved in dichloromethane and washed sequentially with 2N aqueous hydrochloric acid solution and saturated aqueous sodium bicarbonate solution. The organic phase was separated, dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure. The crude product was chromatographed on silica gel eluting with 2%, by volume, methanol/dichloromethane to give the title compound (2.07g) as a colourless oil.

$^1\text{H-NMR}$ (CDCl_3): δ = 7.75 (2H, m), 7.61 (2H, s), 7.50 (1H, s), 7.32 (1H, m), 4.80 (1H, d), 4.35 (1H, m), 3.50-3.90 (7H, m), 3.10-3.30 (2H, m), 2.29 (1H, m), 1.80-2.10 (3H, m), 1.61 (1H, m), 1.40 (1H, m) ppm.

LRMS m/z = 570 (m) $^+$.

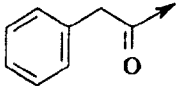
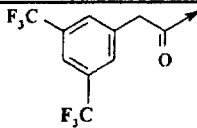
PREPARATIONS 36-37

The compounds of the following tabulated preparations (Table 4) of the general formula:



were prepared by a similar method to that of Preparation 6 using the appropriate 1,3-dioxolanyl protected starting materials.

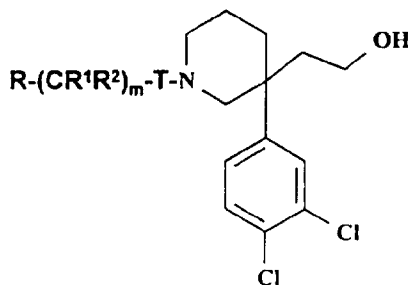
TABLE 4

Prep. no.	Starting material Prep. no.	Stereo-chemistry	R-(CR ¹ R ²) _m -T-	Analytical Data
36	34	S		¹ H-NMR (CDCl ₃): δ = 9.45 (1H,s), 7.10-7.49 (8H,m), 4.23 (1H,d), 3.60-3.38 (3H,m), 3.30-3.50 (2H,m), 2.50-2.66 (2H,q), 2.15 (1H,m), 1.90 (1H,m), 1.40 (1H,m), 1.30 (1H,m) ppm.
37	35	S		¹ H-NMR (CDCl ₃): δ = 9.43 (1H,s), 7.20-7.80 (6H,m), 4.21 (1H,d), 3.40-3.90 (5H,m), 2.63 (2H,m), 1.50-2.30 (4H,m) ppm. LRMS m/z = 526 (m) ⁺

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PREPARATIONS 38-39

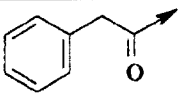
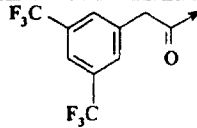
The compounds of the following tabulated preparations (Table 5) of the general formula :



10 were prepared by a similar method to that of Preparation 7 using the appropriate aldehyde starting materials.

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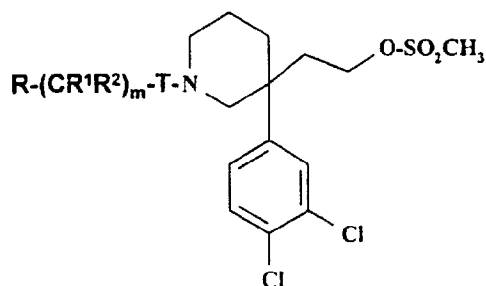
TABLE 5

Prep. no.	Starting material Prep. no.	Stereo-chemistry	R-(CR ¹ R ²) _m -T-	Analytical Data
38	36	S		¹ H-NMR (CDCl ₃): δ = 7.05-7.43 (8H,m), 4.27 (1H,d), 3.30-3.82 (7H,m), 2.01 (1H,m), 1.63-1.89 (4H,m), 1.40 (1H,m), 1.20 (1H,m) ppm.
39	37	S		¹ H-NMR (CDCl ₃): δ = 7.20-7.80 (6H, m), 4.30 (1H, d), 3.75-3.85 (2H, m), 3.30-3.60 (5H, m), 2.10 (1H, m), 1.40-1.90 (6H, m) ppm. LRMS m/z = 528 (m) ⁺

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PREPARATIONS 40-41

The compounds of the following tabulated preparations (Table 6) of the general formula :

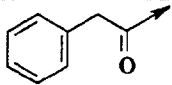
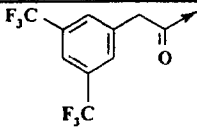


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were prepared by a similar method to that of Preparation 8 using the appropriate alcohol starting materials.

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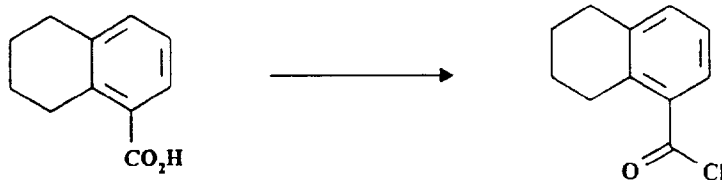
TABLE 6

Prep. no.	Starting material Prep. no.	Stereo-chemistry	R-(CR ¹ R ²) _m -T-	Analytical Data
40	38	S		¹ H-NMR (CDCl ₃): δ = 7.05-7.43 (8H,m), 4.30 (1H,d), 4.00 (1H,m), 3.90 (1H,m), 3.70 (2H,m), 3.30-3.50 (3H,m), 2.91 (3H,s), 2.09 (1H,m), 2.00 (2H,m), 1.80 (1H,m), 1.42 (1H,m), 1.21 (1H,m) ppm.
41	39	S		¹ H-NMR (CDCl ₃): δ = 7.79 (1H,s), 7.62 (2H,s), 7.42 (2H,m), 7.20 (1H,m), 4.29 (1H,d), 3.40-4.00 (7H), 2.90 (3H,s), 2.15 (1H,m), 1.85-2.05 (3H,m), 1.66 (1H,m), 1.50 (1H,m) ppm.

86

PREPARATION 421,2,3,4-Tetrahydronaphth-5-oyl chloride

5

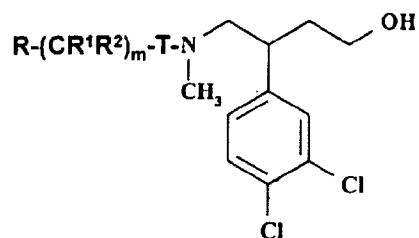


10

1,2,3,4-Tetrahydronaphth-5-oic acid (1.4g) (see Org. Prep. & Proc. Int., 1973, 285) was suspended in anhydrous dichloromethane (10ml) and oxalyl chloride (1.6g) added followed by dimethylformamide (1 drop). The mixture was stirred at room temperature for 1 hour before removal of the solvent under reduced pressure. The resulting residue was dissolved in dichloromethane and the solvent removed under reduced pressure. The residue was again dissolved in dichloromethane and the solvent removed under reduced pressure to give the title compound as an oil (1.5g).

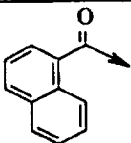
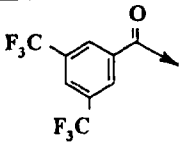
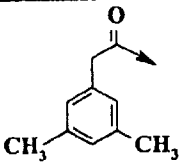
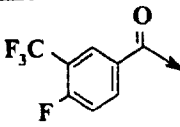
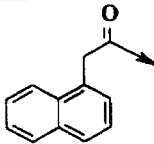
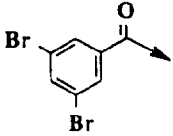
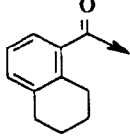
PREPARATIONS 43-49

The compounds of the following tabulated preparations (Table 7) of the general
5 formula:



were prepared by a similar method to that of Preparation 15 using either (R/S)-
or (S)-3-(3,4-dichlorophenyl)-4-(N-methylamino)butan-1-ol and the appropriate
10 acid chloride starting materials.

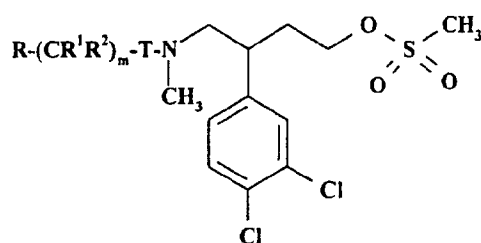
TABLE 7

Prep. no.	Acid chloride starting material	Stereo-chemistry	R-(CR ¹ R ²) _m -T-	Analytical Data
43	1-naphthoyl chloride	R/S		¹ H-NMR (CDCl ₃): δ = 7.20-7.90 (10H,m), 3.00-3.72 (6H,m), 2.57 (3H,s), 1.80-2.03 (2H,m) ppm.
44	3,5-bis-(trifluoromethyl)-benzoyl chloride	R/S		¹ H-NMR (CDCl ₃): δ = 7.88 (1H,s), 7.59 (2H,s), 7.35-7.45 (2H,m), 7.19 (1H,m), 3.00-3.95 (5H,m), 2.71 (3H,s), 1.80-2.05 (2H,m), 1.61 (1H,s) ppm.
45	3,5-dimethyl-phenyl-acetyl chloride	R/S		¹ H-NMR (CDCl ₃): δ = 7.25-7.35 (2H,m), 7.01 (1H,dd), 6.89 (1H,s), 6.79 (2H,s), 3.91 (1H,dd), 3.10-3.70 (6H,m), 2.74 (3H,s), 2.29 (6H,s), 1.70-1.95 (3H,m) ppm.
46	4-fluoro-3-trifluoromethyl-benzoyl chloride	S		¹ H-NMR (CDCl ₃): δ = 7.10-7.50 (6H,m), 3.00-3.95 (5H,m), 2.73 (3H,s), 1.70-2.05 (3H,m), ppm.
47	1-naphthyl-acetyl chloride	R/S		¹ H-NMR (CDCl ₃): δ = 6.90-7.90 (10H,m), 2.90-4.10 (7H,m), 2.79 (3H,s), 1.70-1.90 (3H,m) ppm.
48	3,5-dibromo-benzoyl chloride	R/S		¹ H-NMR (CDCl ₃): δ = 7.00-7.80 (6H,m), 3.00-3.90 (5H,m), 2.70 (3H,s), 1.60-2.10 (3H,m) ppm.
49	see Prep. 42	R/S		¹ H-NMR (CDCl ₃): δ = 6.80-7.45 (6H,m), 3.00-4.00 (6H,m), 2.68-2.83 (4H,m), 2.57 (3H,s), 2.30-2.40 (1H,m), 1.60-2.05 (5H,m) ppm.

89

PREPARATIONS 50-56

The compounds of the following tabulated preparations (Table 8) of the general
 5 formula:

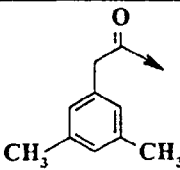
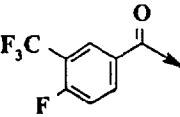
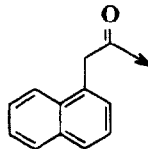
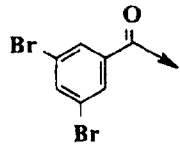
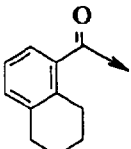


were prepared by a similar method to that of Preparation 19 using the
 appropriate alcohol starting material.

10

TABLE 8

Prep. no.	Starting material Prep. no.	Stereo-chemistry	R-(CR¹R²)ₘ-T-	Analytical Data
50	43	R/S		¹ H-NMR (CDCl ₃): δ = 7.80-7.85 (2H,m), 7.20-7.60 (8H,m), 4.25 (1H,m), 3.70-4.10 (2H,m), 3.13-3.47 (2H,m), 3.00 (3H,s), 2.85 (0.75H,s), 2.61 (2.25H,s), 2.25-2.35 (1H,m), 2.05-2.15 (1H,m) ppm.
51	44	R/S		¹ H-NMR (CDCl ₃): δ = 7.90 (1H,s), 7.61 (2H,s), 7.35-7.48 (2H,m), 7.19 (1H,m), 4.26 (1H,m), 3.60-4.10 (3H,m), 3.37 (1H,m), 2.95 (3H,s), 2.78 (3H,s), 2.25 (1H,m), 2.05 (1H,m) ppm.

52	45	R/S		¹ H-NMR (CDCl ₃): δ = 7.32 (1H, d), 7.26 (1H, s), 7.01 (1H, dd), 6.90 (1H, s), 6.78 (2H, s), 4.14 (1H, m), 3.98 (1H, m), 3.85 (1H, dd), 3.56 (2H, s), 3.35 (1H, dd), 3.16 (1H, m), 2.90 (3H, s), 2.79 (3H, s), 2.29 (6H, s), 2.10 (1H, m), 1.95 (1H, m) ppm.
53	46	S		¹ H-NMR (CDCl ₃): δ = 7.10-7.50 (6H, m), 3.83-4.30 (3H, m), 3.60 (1H, dd), 3.31 (1H, m), 2.99 (3H, s), 2.80 (3H, s), 2.00-2.30 (2H, m) ppm.
54	47	R/S		¹ H-NMR (CDCl ₃): δ = 7.00-7.90 (10H, m), 3.90-4.20 (4H, m), 3.75 (1H, m), 3.59 (1H, m), 3.19 (1H, m), 2.92 (3H, s), 2.82 (3H, s), 2.11 (1H, m), 1.95 (1H, m) ppm.
55	48	R/S		¹ H-NMR (CDCl ₃): δ = 7.00-7.70 (6H, m), 4.23 (1H, m), 4.02 (1H, m), 3.87 (1H, m), 3.58 (1H, m), 3.30 (1H, m), 2.98 (3H, s), 2.74 (3H, t), 2.05-2.25 (2H, m) ppm.
56	49	R/S		¹ H-NMR (CDCl ₃): δ = 6.80-7.50 (6H, m), 4.21 (1H, m), 4.06 (1H, m), 3.30-3.90 (3H, m), 3.00 (3H, s), 2.74 (3H, m), 2.63 (3H, s), 2.05-2.30 (2H, m), 1.70-1.90 (5H, m) ppm.

91

PREPARATION 572,3-Dihydrobenzo[b]furan-7-oic acid

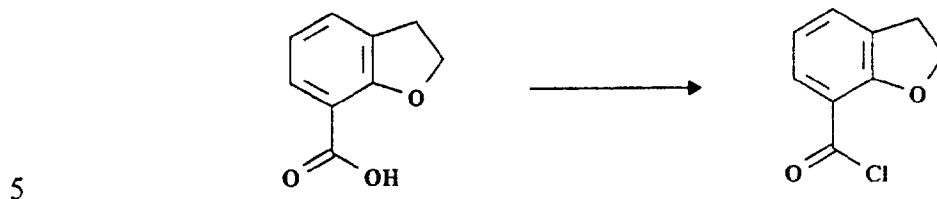
5

N,N,N',N'-Tetramethylethylenediamine (38ml) was dissolved in hexane (300ml), cooled in an ice-bath and n-butyllithium (100ml of a 2.5M solution in hexane) added. The mixture was stirred at 0°C for 15 minutes before adding 2,3-
10 dihydrobenzo[b]furan (30g), dropwise, over 30 minutes. The mixture was allowed to warm to room temperature over 30 minutes, stirred at room temperature for 4 hours, poured onto an excess of solid carbon dioxide and left to stand for 3 days by which time the solvent has evaporated off. The residue was partitioned between ethyl acetate (1L) and 4N aqueous hydrochloric acid
15 solution (240ml), the layers were separated and the aqueous layer extracted with ethyl acetate (500ml). The organic extracts were combined, dried over anhydrous sodium sulphate and the solvent removed under reduced pressure. The residue was then triturated with diethyl ether to give 2,3-dihydrobenzo[b]furan-7-oic acid as a white solid (21g).

20

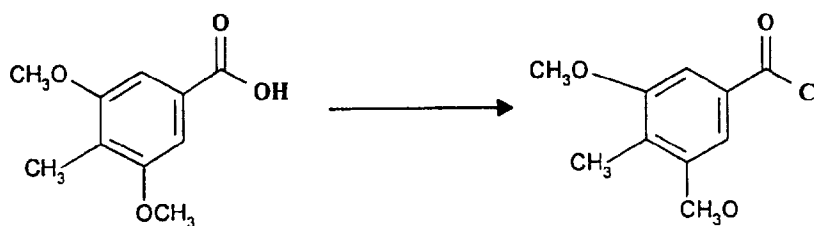
¹H-NMR (CDCl₃): δ = 7.75 (1H, d), 7.31 (1H, d), 6.88 (1H, t), 4.69 (2H, t), 3.20 (2H, t) ppm.

92

PREPARATION 582,3-Dihydrobenzo[b]furan-7-oyl chloride

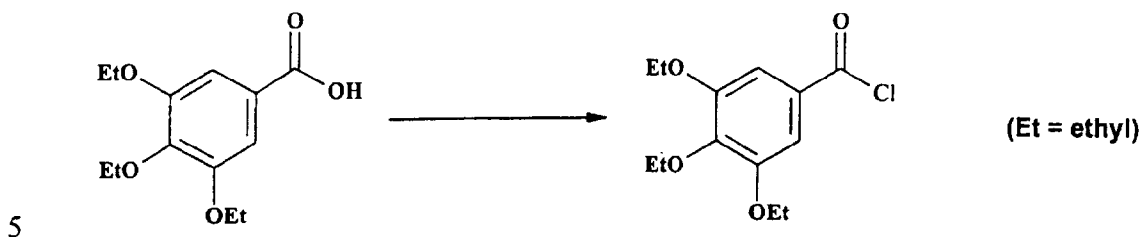
The title compound was prepared from 2,3-dihydrobenzo[b]furan-7-oic acid (see Preparation 57) following the procedure described in Preparation 11.

10

PREPARATION 593,5-Dimethoxy-4-methylbenzoyl chloride

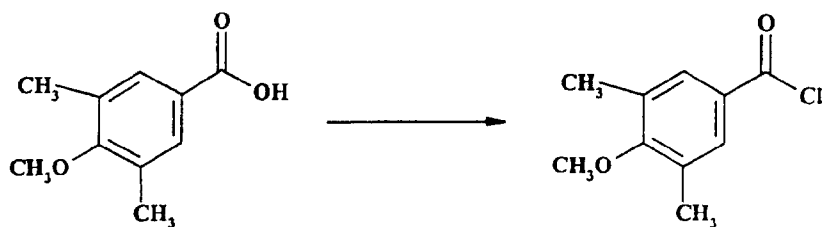
15 The title compound was prepared from 3,5-dimethoxy-4-methylbenzoic acid following the procedure described in Preparation 11.

93

PREPARATION 603,4,5-Triethoxybenzoyl chloride

The title compound was prepared from 3,4,5-triethoxybenzoic acid following the procedure described in Preparation 11.

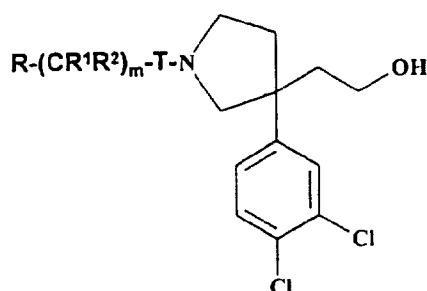
10

PREPARATION 613,5-Dimethyl-4-methoxybenzoyl chloride

15 The title compound was prepared from 3,5-dimethyl-4-methoxybenzoic acid following the procedure described in Preparation 11.

PREPARATIONS 62-71

The compounds of the following tabulated preparations (Table 9) of the general
 5 formula:

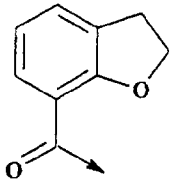
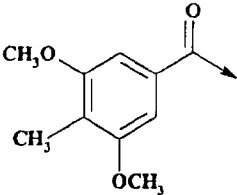
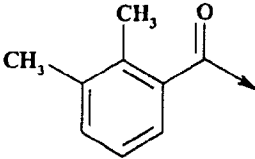
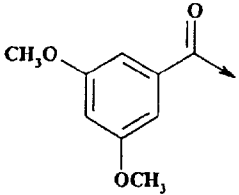
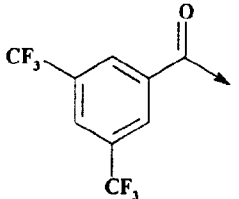
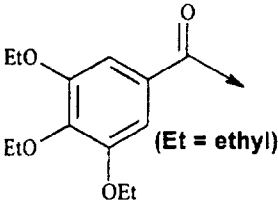


were prepared by a similar method to that of Preparation 12 using 3-(3,4-dichlorophenyl)-3-(2-hydroxyethyl)pyrrolidine hydrochloride (see Preparation 10) and the appropriate acid chlorides as starting materials.

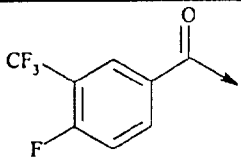
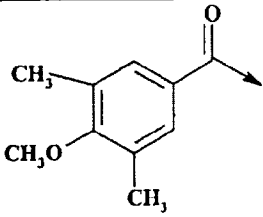
10

TABLE 9

Prep. no.	Acid chloride starting material	R-(CR¹R²)ₘ-T-	Analytical Data
62	3,5-dimethyl-phenylacetyl chloride		¹ H-NMR (CDCl₃): δ = 7.16-7.38 (3H,m), 6.86 (3H,m), 3.32-3.74 (8H,m), 1.85-2.30 (10H,m) ppm.
63	3,4-dimethoxy-benzoyl chloride		¹ H-NMR (CDCl₃): δ = 6.82-7.44 (6H,m), 3.32-3.97 (12H,m), 2.10-2.34 (2H,m), 1.84-2.05 (2H,m) ppm.

64	2,3-dihydro-benzo[b]-furan-7-oyl chloride (see Prep. 58)		¹ H-NMR (CDCl ₃): δ = 7.12-7.42 (5H,m), 6.87 (1H,m), 4.60 (2H,t), 2.84-4.02 (9H,m), 1.89-2.30 (3H,m) ppm.
65	3,5-dimethoxy-4-methyl-benzoyl chloride (see Prep. 59)		¹ H-NMR (CDCl ₃): δ = 7.40 (1H,m), 7.00-7.26 (2H,m), 6.65 (2H,d), 3.28-4.04 (12H,m), 2.28 (2H,m), 2.12 (3H,d), 1.86-2.32 (2H,m) ppm.
66	2,3-dimethyl-benzoyl chloride		¹ H-NMR (CDCl ₃): δ = 6.87-7.46 (6H,m), 3.00-4.17 (6H,m), 1.86-2.35 (10H,m) ppm.
67	3,5-dimethoxy-benzoyl chloride		¹ H-NMR (CDCl ₃): δ = 7.00-7.44 (3H,m), 6.57 (3H,m), 3.34-4.06 (12H,m), 1.88-2.34 (4H,m) ppm.
68	3,5-bis-(trifluoromethyl)-benzoyl chloride		¹ H-NMR (CDCl ₃): δ = 7.97 (3H,m), 6.95-7.48 (3H,m), 3.80-4.10 (3H,m), 3.30-3.68 (3H,m), 1.90-2.37 (4H,m) ppm.
69	3,4,5-triethoxy-benzoyl chloride (see Prep. 60)		¹ H-NMR (CDCl ₃): δ = 6.98-7.45 (3H,m), 6.70 (2H,d), 4.10 (6H,m), 3.28-3.80 (5H,m), 3.05 (2H,m), 1.90-2.30 (4H,m), 1.40 (9H,m) ppm.

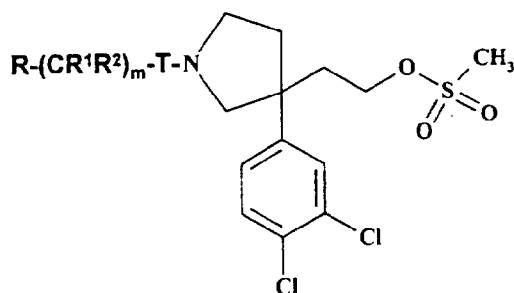
96

70	4-fluoro-3-trifluoromethylbenzoyl chloride		$^1\text{H-NMR}$ (CDCl_3): δ = 7.82 (1H, m), 7.62 (1H, m), 7.13-7.45 (4H, m), 3.30-4.06 (6H, m), 1.91-2.34 (4H, m) ppm.
71	3,5-dimethyl-4-methoxybenzoyl chloride (see Prep. 61)		$^1\text{H-NMR}$ (CDCl_3): δ = 7.20-7.44 (3H, m), 7.15 (2H, m), 3.30-4.00 (9H, m), 2.28 (6H, d), 2.14 (2H, m), 1.95 (2H, m) ppm.

PREPARATIONS 72-81

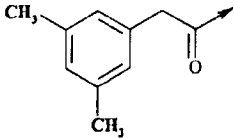
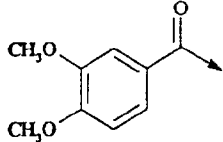
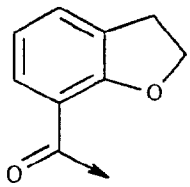
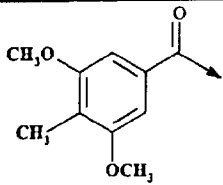
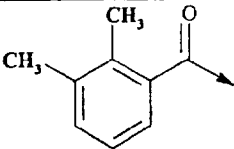
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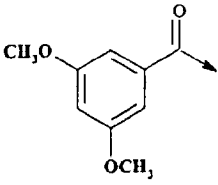
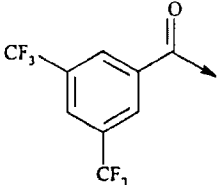
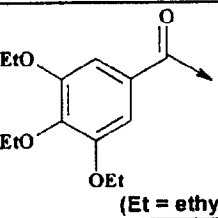
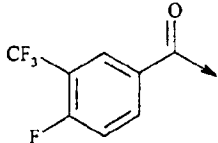
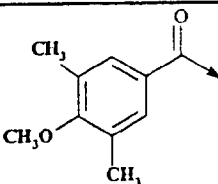
The compounds of the following tabulated preparations (Table 10) of the general formula:



10 were prepared by a similar method to that of Preparation 13 using the appropriate alcohol as starting material.

TABLE 10

Prep. no.	Starting material Prep. no.	R-(CR ¹ R ²) _m -T-	Analytical Data
72	62		¹ H-NMR (CDCl ₃): δ = 7.04-7.42 (3H,m), 6.86 (3H,m), 3.73-3.98 (3H,m), 3.51-3.65 (3H,m), 3.40 (1H,m), 2.87 (4H,m), 1.99-2.30 (10H,m) ppm.
73	63		¹ H-NMR (CDCl ₃): δ = 7.45 (1H,d), 7.06-7.26 (4H,m), 6.88 (1H,m), 3.46-4.02 (12H,m), 2.88 (3H,s), 2.12-2.22 (4H,m) ppm.
74	64		¹ H-NMR (CDCl ₃): δ = 7.41 (1H,m), 7.02-7.30 (4H,m), 6.90 (1H,m), 4.63 (2H,m), 3.36-4.06 (6H,m), 3.24 (2H,t), 3.92 (1.5H,s), 2.80 (1.5H,s), 2.01 (4H,m) ppm.
75	65		¹ H-NMR (CDCl ₃): δ = 7.45 (1H,m), 7.22 (1H,d), 7.16 (0.5H,d), 7.00 (0.5H,d), 6.65 (2H,d), 3.40-4.02 (12H,m), 2.95 (1.5H,s), 2.82 (1.5H,s), 2.14-2.39 (4H,m), 2.10 (3H,d) ppm.
76	66		¹ H-NMR (CDCl ₃): δ = 7.46 (1H,m), 6.98-7.26 (5H,m), 3.05-4.14 (6H,m), 2.95 (1.5H,s), 2.82 (1.5H,s), 2.15-2.34 (10H,m) ppm.

77	67		¹ H-NMR (CDCl ₃): δ = 7.45 (1H,m), 7.23 (1H,d), 7.16 (0.5H,d), 7.08 (3H,m), 7.00 (0.5H,d), 3.39-4.02 (6H,m), 2.94 (1.5H,s), 2.81 (1.5H,s), 2.06-2.39 (10H,m) ppm.
78	68		¹ H-NMR (CDCl ₃): δ = 7.97 (3H,m), 6.95-7.48 (3H,m), 3.38-4.08 (6H,m), 2.96 (1.5H,s), 2.84 (1.5H,s), 2.12-2.42 (4H,m) ppm.
79	69		¹ H-NMR (CDCl ₃): δ = 7.00-7.48 (3H,m), 6.70 (2H,s), 3.40-4.15 (12H,m), 2.94 (1.5H,s), 2.82 (1.5H,s), 2.08-2.36 (4H,m), 1.39 (9H,m) ppm.
80	70		¹ H-NMR (CDCl ₃): δ = 7.82 (1H,m), 7.72 (1H,m), 6.96-7.50 (4H,m), 3.53-4.10 (6H,m), 2.95 (1.5H,s), 2.85 (1.5H,s), 2.10-2.38 (4H,m) ppm.
81	71		¹ H-NMR (CDCl ₃): δ = 7.48 (1H,m), 7.24 (1H,d), 7.17 (3H,m), 3.55-4.04 (9H,m), 2.95 (1.5H,s), 2.83 (1.5H,s), 2.08-2.36 (10H,m) ppm.

COMPARATIVE PHARMACOLOGICAL DATA

5 The NK₁ and NK₂ receptor antagonist activities of a selection of the
compounds of the preceding Examples, the compound of Example 1 of EP-A-
0591040, the racemic mixture of the compounds of Examples 4 and 10 of EP-
A-0591040 and the compound of Example 31 of EP-A-0714891 were
determined by the methods described on pages 25 and 26.

10 The results are shown in Tables A and B. A value of "6.0" represents
very weak activity. A difference in values of one log.unit corresponds to a 10-
fold activity difference.

TABLE A

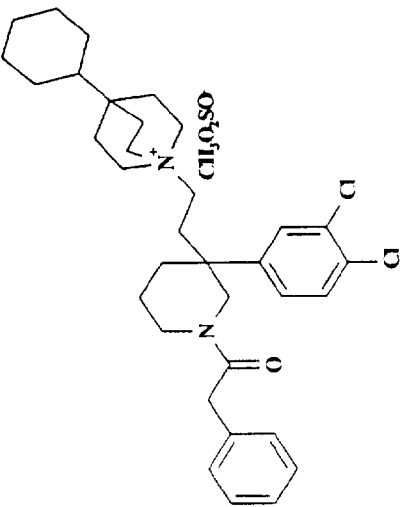
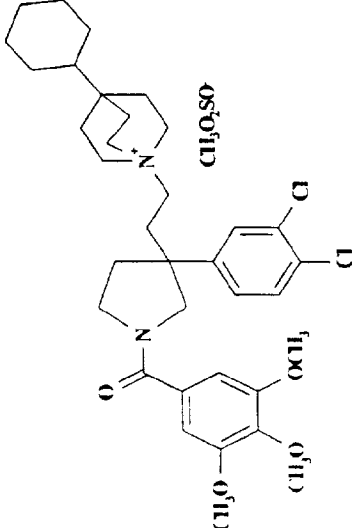
Structure	Stereo-chemistry	Example No.	NK ₁ activity (pK _b or pA ₂)	NK ₂ activity (pK _b or pA ₂)
	R/S	1	7.1	6.7
	R/S	2	6.9	6.8

TABLE A (continued)

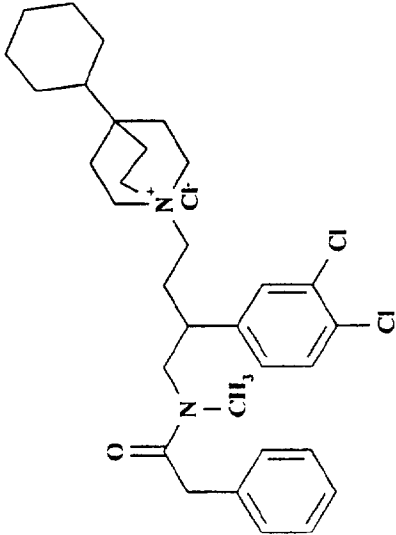
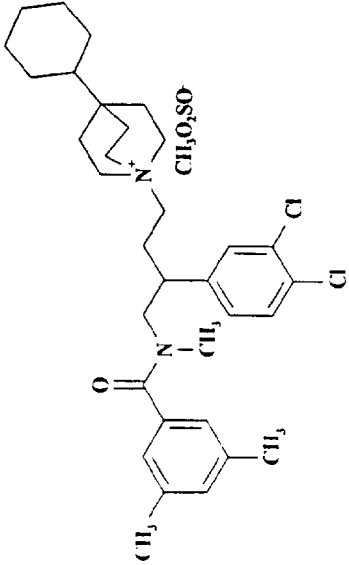
Structure	Stereo-chemistry	Example No.	NK ₁ activity (pK _b or pA ₂)	NK ₂ activity (pK _b or pA ₂)
	R/S	3	6.5	6.5
	R/S	4	7.0	6.7

TABLE A (continued)

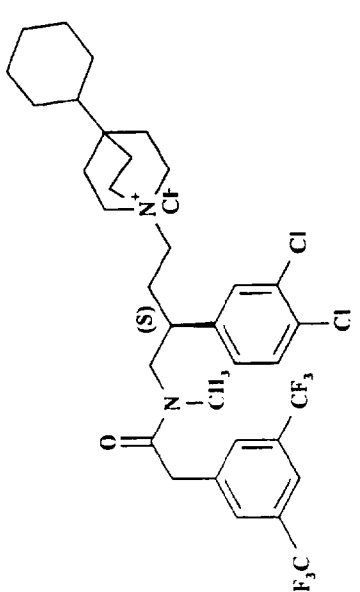
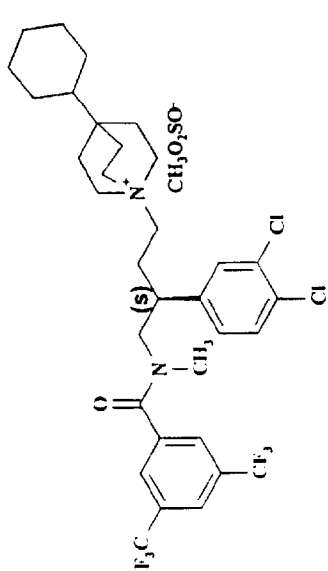
Structure	Stereo-chemistry	Example No.	NK ₁ activity (pK _b or pA ₂)	NK ₂ activity (pK _b or pA ₂)
	S	5	7.0	6.9
	S	6	7.3	7.3

TABLE A (continued)

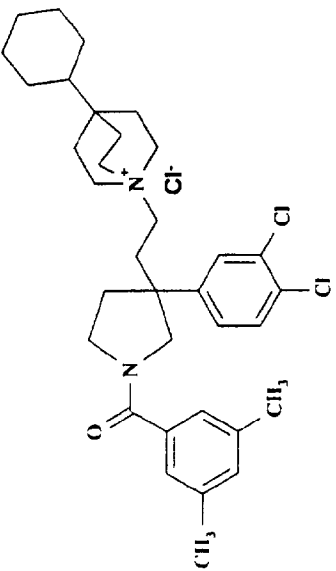
Structure	Stereo-chemistry	Example No.	NK ₁ activity (pK _b or pA ₂)	NK ₂ activity (pK _b or pA ₂)
	R/S	7	7.0	7.1

TABLE B

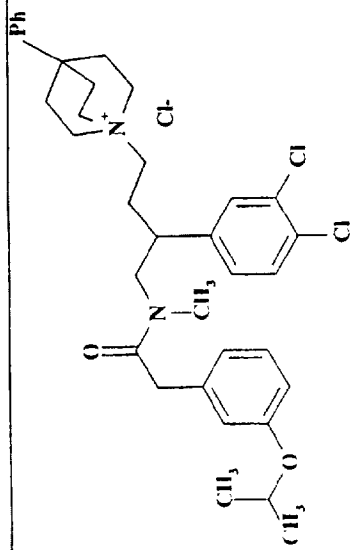
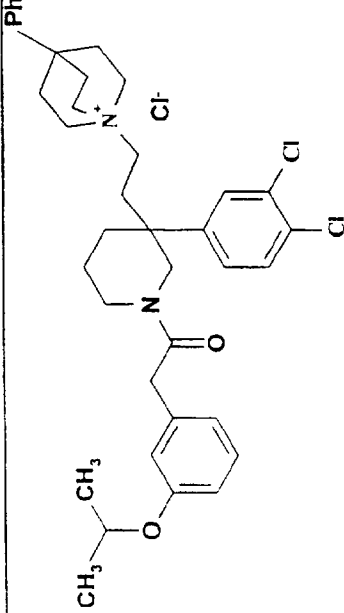
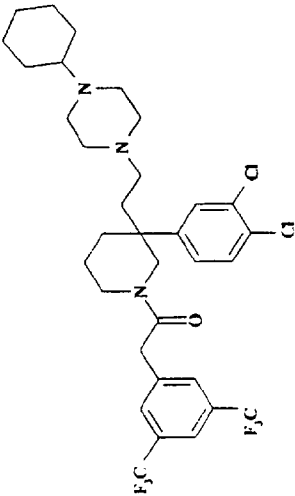
Structure	Stereo-chemistry	Reference	NK ₁ activity (pK _b or pA ₂)	NK ₂ activity (pK _b or pA ₂)
	R/S	Example 1 of EP-A- 0591040	7.6	6.0
	R/S	Racemate of Examples 4 and 10 of EP-A- 0591040	>7.5	<6

TABLE B (continued)

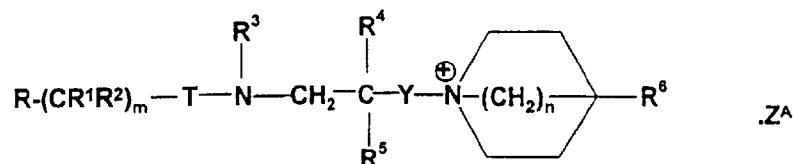
Structure	Stereo-chemistry	Reference	NK ₁ activity (pK _b or pA ₂)	NK ₂ activity (pK _b or pA ₂)
	S	Example 31 of EP-A- 0714891	6.0	<6

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CLAIMS

1. A compound of the formula:

5



(I)

wherein R is phenyl, C₃-C₇ cycloalkyl or heteroaryl, each of which being optionally benzo- or C₃-C₇ cycloalkyl-fused and optionally substituted, including in the benzo- or C₃-C₇ cycloalkyl-fused portion, by from 1 to 3 substituents each independently selected from C₁-C₄ alkyl, fluoro(C₁-C₄)alkyl, C₁-C₄ alkoxy, fluoro(C₁-C₄)alkoxy, C₂-C₄ alkanoyl, halo, C₁-C₄ alkoxy carbonyl, C₃-C₇ cycloalkyl, -S(O)_p(C₁-C₄ alkyl), cyano, -NR⁷R⁸, -S(O)_pNR⁷R⁸, -NR⁷(C₁-C₄ alkanoyl) and -CONR⁷R⁸, or R is 2,3-dihydrobenzo[b]furanyl or chromanyl;

R¹ and R² are either each independently selected from H and C₁-C₆ alkyl or, when taken together, represent C₂-C₆ alkylene;

R³ and R⁴ are either each independently selected from H and C₁-C₆ alkyl or, when taken together, represent unbranched C₁-C₄ alkylene;

R⁵ is phenyl, naphthyl, benzyl, thienyl, benzo[b]thienyl or indolyl, each of which being optionally substituted by from 1 to 3 substituents each independently selected from C₁-C₄ alkyl, fluoro(C₁-C₄)alkyl, C₁-C₄ alkoxy, halo and cyano, or R⁵ is 1,3-benzodioxolan-4 or 5-yl or 1,4-benzodioxan-5 or 6-yl;

R^6 is C_3 - C_7 cycloalkyl optionally substituted by from 1 to 3 substituents each independently selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halo, cyano, fluoro(C_1 - C_4)alkyl and fluoro(C_1 - C_4)alkoxy;

5

R^7 and R^8 are either each independently selected from H and C_1 - C_4 alkyl or, when taken together, represent C_4 - C_6 alkylene;

T is carbonyl;

10

Y is unbranched C_2 - C_4 alkylene;

Z^A is a pharmaceutically acceptable anion;

15

m is 0 or 1;

n is 1 or 2;

p is 0, 1 or 2; and

20

"heteroaryl", used in the definition of R, means thienyl or a 5- or 6-membered ring heteroaryl group containing either from 1 to 4 nitrogen heteroatoms, or 1 or 2 nitrogen heteroatom(s) and 1 oxygen or sulphur heteroatom,

25

with the proviso that when m is 0 and R is optionally fused and optionally substituted heteroaryl, said heteroaryl is linked by a ring carbon atom to T.

2. A compound as claimed in claim 1 wherein R is phenyl, optionally benzo- or C₃-C₇ cycloalkyl-fused, and optionally substituted, including in the benzo- or C₃-C₇ cycloalkyl-fused portion, by from 1 to 3 substituents
5 each independently selected from C₁-C₄ alkyl, halo, fluoro(C₁-C₄)alkyl and C₁-C₄ alkoxy, or R is 2,3-dihydrobenzo[b]furanyl.
3. A compound as claimed in claim 1 or 2 wherein R is phenyl, naphthyl or 1,2,3,4-tetrahydronaphthyl, each of which being optionally substituted by
10 from 1 to 3 substituents each independently selected from methyl, fluoro, bromo, trifluoromethyl, methoxy and ethoxy, or R is 2,3-dihydrobenzo[b]furanyl.
4. A compound as claimed in any preceding claim wherein R is 3,5-
15 bis(trifluoromethyl)phenyl or 3,5-dimethylphenyl.
5. A compound as claimed in any preceding claim wherein R¹ and R² are H.
6. A compound as claimed in any preceding claim wherein either R³ is C₁-
20 C₄ alkyl and R⁴ is H, or R³ and R⁴, when taken together, represent C₂-C₃ alkylene.
7. A compound as claimed in any preceding claim wherein either R³ is methyl and R⁴ is H, or R³ and R⁴, when taken together, represent 1,2-
25 ethylene or 1,3-propylene.
8. A compound as claimed in any preceding claim wherein R⁵ is phenyl optionally substituted by 1, 2 or 3 halo substituents.
- 30 9. A compound as claimed in any preceding claim wherein R⁵ is 3,4-dichlorophenyl.

10. A compound as claimed in any preceding claim wherein R⁶ is cyclohexyl optionally substituted by from 1 to 3 substituents each independently selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, cyano, fluoro(C₁-C₄)alkyl and fluoro(C₁-C₄)alkoxy.
11. A compound as claimed in any preceding claim wherein R⁶ is cyclohexyl.
12. A compound as claimed in any preceding claim wherein Y is 1,2-ethylene.
13. A compound as claimed in any preceding claim wherein Z^A is chloride or methanesulphonate.
14. A compound as claimed in any preceding claim wherein m is 0.
15. A compound as claimed in any preceding claim wherein n is 2.
16. A compound as claimed in claim 1 which is selected from the group consisting of:
- (i) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-phenylacetyl]piperidin-3-yl]ethyl)quinuclidinium methanesulphonate;
 - (ii) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,4,5-trimethoxybenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium methanesulphonate;
 - (iii) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methylphenylacetamido]butyl)quinuclidinium chloride;
 - (iv) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-3,5-dimethylbenzamido]butyl)quinuclidinium methanesulphonate;

- (v) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-3,5-bis(trifluoromethyl)phenylacetamido]butyl)quinuclidinium chloride;
- (vi) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-3,5-bis-(trifluoromethyl)benzamido]butyl)quinuclidinium
methanesulphonate;
- (vii) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,5-dimethylbenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride;
- (viii) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methylnaphthalene-1-carboxamido]butyl)quinuclidinium methanesulphonate;
- (ix) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-3,5-dimethylphenylacetamido]butyl)quinuclidinium
methanesulphonate;
- (x) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-4-fluoro-3-trifluoromethylbenzamido]butyl)quinuclidinium
methanesulphonate;
- (xi) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,5-bis(trifluoromethyl)phenylacetyl)piperidin-3-yl]ethyl)quinuclidinium
methanesulphonate;
- (xii) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,5-bis(trifluoromethyl)benzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium
chloride;
- (xiii) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,5-dimethylphenylacetyl)pyrrolidin-3-yl]ethyl)quinuclidinium
methanesulphonate;
- (xiv) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,4-dimethoxybenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride;

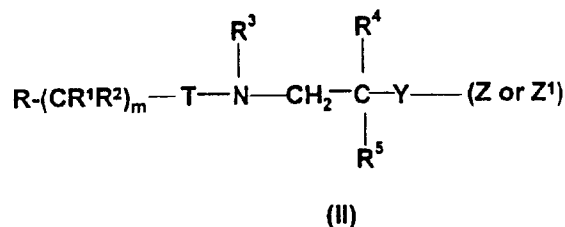
- (xv) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,5-dimethoxy-4-methylbenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride;
- (xvi) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(2,3-dihydrobenzo[b]furan-7-carbonyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride;
- (xvii) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(2,3-dimethylbenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride;
- (xviii) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methylnaphthalene-1-acetamido]butyl)quinuclidinium methanesulphonate;
- (xix) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-3,5-dibromobenzamido]butyl)quinuclidinium methanesulphonate;
- (xx) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-1,2,3,4-tetrahydronaphthalene-5-carboxamido]butyl)quinuclidinium methanesulphonate;
- (xxi) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-3,5-bis(trifluoromethyl)benzamido]butyl)-1-azoniabicyclo[2.2.1]heptane methanesulphonate;
- (xxii) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,5-dimethoxybenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride;
- (xxiii) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,4,5-triethoxybenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride;
- (xxiv) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(4-fluoro-3-trifluoromethylbenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride;
- (xxv) 4-cyclohexyl-1-(2-[3-(3,4-dichlorophenyl)-1-(3,5-dimethyl-4-methoxybenzoyl)pyrrolidin-3-yl]ethyl)quinuclidinium chloride; and
- (xxvi) 4-cyclohexyl-1-(3-[3,4-dichlorophenyl]-4-[N-methyl-3,5-bis(trifluoromethyl)benzamido]butyl)quinuclidinium chloride;
- and the alternative pharmaceutically acceptable salts thereof (re Z^A), and the individual (R)- and (S)- stereoisomers of any thereof.

17. A compound as claimed in claim 1 which is selected from the group consisting of:
- 5 (i) 4-cyclohexyl-1-(3(S)-[3,4-dichlorophenyl]-4-[N-methyl-3,5-bis-(trifluoromethyl)benzamido]butyl)quinuclidinium methanesulphonate; and
- (ii) 4-cyclohexyl-1-(3(S)-[3,4-dichlorophenyl]-4-[N-methyl-3,5-bis-(trifluoromethyl)benzamido]butyl)quinuclidinium chloride.
- 10 18. A pharmaceutical composition comprising a compound of the formula (I) as claimed in any preceding claim, together with a pharmaceutically acceptable diluent or carrier.
- 15 19. A compound of the formula (I) or a pharmaceutically acceptable composition thereof, as claimed in any one of claims 1 to 17 and 18 respectively, for use as a medicament.
- 20 20. The use of a compound of the formula (I), or of a pharmaceutically acceptable composition thereof, as claimed in any one of claims 1 to 17 and 18 respectively, for the manufacture of a medicament for the treatment of a disease by producing an antagonist effect on a tachykinin receptor or on a combination of tachykinin receptors.
- 25 21. Use as claimed in claim 20 where the antagonist effect is on the human NK₁ and NK₂ tachykinin receptors.
- 30 22. Use as claimed in claim 20 or 21 where the disease is an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-

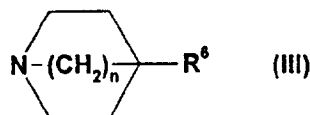
- oesophageal reflux, faecal incontinence, colitis or Crohn's disease, a disease caused by Helicobacter pylori or another urease-positive Gram negative bacteria, a urogenital tract disorder such as incontinence, hyperreflexia or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis, atopic dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, emesis, cough, migraine or acute or chronic pain.
23. A method of treatment of a human to treat a disease by producing an antagonist effect on a tachykinin receptor or on a combination of tachykinin receptors, which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable composition thereof, as claimed in any one of claims 1 to 17 and 18, respectively.
24. A method as claimed in claim 23 where the antagonist effect is on the human NK₁ and NK₂ tachykinin receptors.
25. A method as claimed in claim 23 or 24 where the disease is an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, a disease caused by Helicobacter pylori or another urease-

positive Gram negative bacteria, a urogenital tract disorder such as incontinence, hyperreflexia or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis, atopic dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, emesis, cough, migraine or acute or chronic pain.

26. A process for the preparation of a compound of the formula (I) as claimed in claim 1 comprising reaction of a compound of the formula:



wherein R, R¹, R², R³, R⁴, R⁵, T, Y and m are as defined for a compound of the formula (I) in claim 1, Z is a leaving group capable of forming a pharmaceutically acceptable anion (Z^A) and Z¹ is a leaving group, with a compound of the formula:

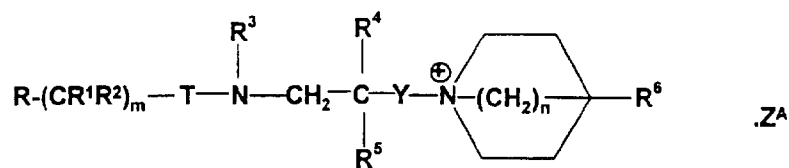


wherein R⁶ and n are as previously defined for a compound of the formula (I) in claim 1: said process being followed by either (a), where Z¹ is a suitable leaving group, exchange for a pharmaceutically acceptable

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anion (Z^A), or (b), optionally, where Z^A is a pharmaceutically acceptable anion, exchange for another pharmaceutically acceptable anion.

- 5 27. A compound of the formula:



(I)

wherein R is phenyl, C₃-C₇ cycloalkyl or heteroaryl, each of which being
 10 optionally benzo- or C₃-C₇ cycloalkyl-fused and optionally substituted,
 including in the benzo- or C₃-C₇ cycloalkyl-fused portion, by from 1 to 3
 substituents each independently selected from C₁-C₄ alkyl, fluoro(C₁-
 C₄)alkyl, C₁-C₄ alkoxy, fluoro(C₁-C₄)alkoxy, C₂-C₄ alkanoyl, halo, C₁-C₄
 alkoxy carbonyl, C₃-C₇ cycloalkyl, -S(O)_p(C₁-C₄ alkyl), cyano, -NR⁷R⁸,
 15 -S(O)_pNR⁷R⁸, -NR⁷(C₁-C₄ alkanoyl) and -CONR⁷R⁸, or R is 2,3-
 dihydrobenzo[b]furanyl or chromanyl;

R¹ and R² are either each independently selected from H and C₁-C₆ alkyl
 or, when taken together, represent C₂-C₆ alkylene;

20

R³ and R⁴ are either each independently selected from H and C₁-C₆ alkyl
 or, when taken together, represent unbranched C₁-C₄ alkylene;

R⁵ is phenyl, naphthyl, benzyl, thienyl, benzo[b]thienyl or indolyl, each of which being optionally substituted by from 1 to 3 substituents each independently selected from C₁-C₄ alkyl, fluoro(C₁-C₄)alkyl, C₁-C₄ alkoxy, halo and cyano, or R⁵ is 1,3-benzodioxolan-4 or 5-yl or 1,4-benzodioxan-5 or 6-yl;

R⁶ is C₃-C₇ cycloalkyl optionally substituted by from 1 to 3 substituents each independently selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, cyano, fluoro(C₁-C₄)alkyl and fluoro(C₁-C₄)alkoxy;

R⁷ and R⁸ are either each independently selected from H and C₁-C₄ alkyl or, when taken together, represent C₄-C₆ alkylene;

T is carbonyl;

Y is unbranched C₂-C₄ alkylene;

Z^A is a pharmaceutically acceptable anion;

m is 0 or 1;

n is 1 or 2;

p is 0, 1 or 2; and

"heteroaryl", used in the definition of R, means thienyl or a 5- or 6-membered ring heteroaryl group containing either from 1 to 4 nitrogen heteroatoms, or 1 or 2 nitrogen heteroatom(s) and 1 oxygen or sulphur heteroatom.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/04414

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D453/02 C07D487/08 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 591 040 A (SANOFI ELF) 6 April 1994 cited in the application see the whole document	1-27
A	EP 0 714 891 A (LILLY CO ELI) 5 June 1996 cited in the application	1-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

9 December 1997

Date of mailing of the international search report

17. 12. 97

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De Jong, B

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP 97/04414

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 23-25
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 97/04414

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